Safety and Efficacy of
Radial Artery Conduits
for Coronary Artery Bypass Surgery

A thesis submitted for the degree of

DOCTOR OF PHILOSOPHY
by
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“There is no privileged territory. In the abysses of our inner world everything has a meaning. We cannot choose only those things that please us, according to the dictates of our feelings, our imagination, the scientific and philosophical form of our mind. A difficult or obscure subject must not be neglected just because it is difficult and obscure. All methods should be employed. The qualitative is as true as the quantitative. The relations that can be expressed in mathematical terms do not possess greater reality than those that cannot be so expressed. Darwin, Claude Bernard, and Pasteur, whose discoveries could not be described in algebraic formulas, were as great scientists as Newton and Einstein. Reality is not necessarily clear and simple. It is not even sure that we are always able to understand it.”

Alexis Carrel
Man, The Unknown
To My parents:
Mr. Chue Kieo Hao
Mrs. Sujitra Mahatthanaphanit

Patients and volunteers
Supervisors and colleagues

without you
this thesis would not exist
Abstract

Coronary artery bypass grafting (CABG) is the most common cardiac surgical operation performed in western countries, and is also increasingly being performed in developing countries. However the long-term results of CABG using the saphenous vein graft have not been satisfactory. Surgeons have therefore been seeking a better conduit. The radial artery (RA) is a potentially suitable alternative conduit and has to date provided good early results. This thesis investigates the utility of the RA as a coronary artery bypass graft from a number of perspectives. It demonstrates the safety of RA harvesting by examining hand collateral circulation using anatomical dissection, physical examination using the modified Allen test, measuring digital blood pressure, and examining the flow velocity in the digital artery using Doppler ultrasound. Anatomical examinations revealed consistent continuity between the RA and ulnar artery in the hand through either superficial or deep palmar arches. The modified Allen test was found to be useful as a screening test compared with the Doppler dynamic test and digital blood pressure index. A histological comparison was made between pre-existing intimal disease in the RA compared with that in the standard conduit the internal thoracic artery (ITA). The RA showed a higher prevalence and degree of intimal disease than ITA. Risk factors for intimal hyperplasia in the RA were age, diabetes, smoking and peripheral vascular disease. The only predictor for medial calcification was age. Ultrasound was used to examine the RA preoperatively and found to be useful in detecting a significant degree of calcification. However it was not useful to determine the severity of intimal disease in the RA. A cohort of patients who received the RA or the right ITA as a second graft in addition to the left ITA had improved survival rates at median 3 years follow-up compared with patients who received a saphenous vein grafts as a second graft. Early graft patency in a prospective randomized controlled trial, The Australian Radial Artery Study Trial, also showed excellent patency of the radial graft. These findings have led me to the conclusion that the RA is a safe and effective alternative conduit for CABG. To demonstrate more clearly, long-term angiographic follow-up is required.
The studies described in this thesis have not previously been submitted for a degree at this or any other university or tertiary institution. The studies undertaken and their interpretation are my own original work, except where due acknowledgement has been made.

I also declare that the sum total of the words in this thesis, exclusive of tables, figures, bibliography and appendix is less than 100,000 words.

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Publications and Communications

Journal Publications:


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Manuscripts under review

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Improved survival in coronary artery bypass grafting using the radial artery.

Ruengsakulrach P., Brooks M., Sinclair R., Hare DL., Gordon I., Buxton B.
Ultrasound intima-media thickness does not predict histological intimal disease in arteries.

Ruengsakulrach P., Brooks M., Sinclair R., Hare DL., Gordon I., Buxton B.
Comparison of ultrasound and histopathology for detecting calcification in the distal and proximal segments of radial artery grafts.

Buxton B., Ruengsakulrach P., Gordon I., Komeda M., Raman J., Greene L., Wilson G., Hare DL.
Safety of removing the radial artery: Allen test versus digital brachial systolic blood pressure index.
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Preface

The prevention and treatment of coronary heart disease is one of the largest challenges facing the medical profession in the developed world. For instance, in 1996, approximately 200,000 patients presented with coronary artery disease in the United States alone. One of the increasingly common treatment modalities for ischemic heart disease is coronary artery bypass grafting.

An ageing population and the use of angioplasty have resulted in an increasing number of patients requiring multivessel grafting. Until recently, the current practice for multivessel grafting involved using a single internal thoracic artery in combination with the saphenous vein graft. However, while this approach has proven beneficial in the short-term, the long-term outcomes of this operation have been disappointing. In particular, early death, myocardial infarction and recurrent angina have been linked with saphenous vein graft failure and the progression of native coronary artery disease. In contrast with the poor results associated with saphenous vein grafting, the internal thoracic artery has shown excellent long-term results with a graft patency at 10-years of about 95%. As a consequence, surgeons have begun to explore the use of bilateral, sequential and composite internal thoracic artery grafts.

Furthermore, in an attempt to avoid the complications associated with saphenous vein graft failure and to improve long-term survival, some surgeons have abandoned the saphenous vein in favour of complete arterial grafting. The shift towards complete arterial grafting has been hampered, however, by the limited number of conduits available. Increasingly, then, surgeons concerned with finding suitable alternative conduits for grafting have been experimenting with the use of arteries other than the internal thoracic artery. However, most of these have demonstrated limitations, such as, difficulty in harvesting (the splenic artery and the right gastroepiploic artery) and inadequate vessel length and diameter (the inferior epigastric artery). In contrast, an alternative conduit that has a number of
favorable characteristics for bypass grafting is the radial artery.

When the radial artery was initially used in the early 1970s it was soon abandoned due to a high graft failure rate. However, this occurred at a time when there was no knowledge of the importance of the endothelium in controlling graft function. The subsequent discovery that some of the radial artery grafts from the 1970s were patent 15 years later prompted the reevaluation of the radial artery as a conduit for coronary artery bypass grafting. New studies using the radial artery produced surprisingly good patency rates. It was suggested that the improvement may have been the result of the use of calcium channel blockers to control vasospasm.

Although some studies have suggested that the patency rates of radial artery grafts are better than those of the saphenous vein and approach those of the internal thoracic artery, a number of questions remain unanswered. In particular, the feasibility, safety and efficacy of using the radial artery as a coronary artery bypass graft needs to be objectively assessed before it can be confidently used routinely in bypass procedures.
Chapter 1
Introduction

(a) The History of the Development of Coronary Artery Surgery and
The Role of the RA as A Conduit for Coronary Artery Bypass
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Introduction

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“Only the man who is familiar with the art and science of the past is competent to aid in its progress in the future”

Theodor Billroth

Introduction

The history of cardiac surgery provides interesting insights into the development of contemporary surgical procedures. Furthermore, an historical approach may also open up future directions for cardiac surgery. The development of coronary artery surgery has not always progressed in a linear fashion. For example, some major advances have been made by revisiting previous techniques and approaches. Thus, although early surgical attempts to treat ischemic heart disease either failed or achieved marginal results, these pioneering techniques foreshadowed later developments in contemporary cardiac surgery. In the discussion that follows I will outline some of the major techniques developed to treat ischemic heart disease. These techniques are divided into three groups, namely, extracardiac operations for angina, indirect coronary revascularization, and direct coronary revascularization. This will be followed by discussion of the history of the use of the radial artery (RA) as a bypass graft.

While the development of techniques for managing ischemic heart disease also has not always followed a smooth, chronological path, it can be seen as progressing through several reasonably distinct stages — from the development of palliative techniques for the treatment of ischemia and its symptoms, through use of both indirect and direct methods of revascularizing the myocardium, to present day direct coronary artery grafting. I have included an overview of the history of surgery for ischemic heart disease because I believe this history places my own
work in an appropriate historical context. It also provides many useful examples of the ingenuity, tenacity and work needed to achieve progress in a difficult field.

**Extracardiac Operations for Angina**

**Observations and Concepts**

In the late 19th and early 20th centuries, a number of extracardiac approaches to the treatment of angina emerged. Interestingly, the idea of surgical revascularization was first suggested as early as 1880 when Langer observed the interconnections within the coronary system, and between coronary vessels and surrounding extracardiac structures such as the diaphragm, bronchi, and the pericardium. In 1898, Pratt suggested that coronary sinus blood flow could be reversed by the insertion of an artery into the myocardial venous system thereby enhancing myocardial blood flow. Much of the early surgical treatment of ischemic heart disease however, was primarily concerned with relieving the discomfort of angina rather than with revascularizing the myocardium. In 1899 for example, Parisian Professor of Physiology, Charles Emile Francois Franck, suggested treating angina by performing sympathetic ganglionectomy of the upper thoracic ganglia to divide the afferent pain fibres. Another palliative approach for treating angina, namely thyroidectomy, emerged from Kocher’s observation in 1902 that a patient with angina became asymptomatic after total thyroidectomy. Finally, Wearn, who had found connections between the cardiac chambers and the myocardial sinusoids, suggested in 1928 that “if coronary flow was occluded,

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flow in the thebesian vessels could be reversed, thus supplying blood from the ventricular cavities to the myocardium”.5

Sympathectomy

The first operation for ischemic heart disease in humans was carried out by Charles Mayo in 1913 and involved cervical sympathectomy.6 The idea of cervico-thoracic sympathectomy for angina pectoris was put to clinical trial on April 2, 1916, by Thomas Jonnesco of Bucharest. After performing bilateral extirpation of the cervical sympathetic trunk and the first dorsal ganglion he found that the procedure eliminated the symptoms of angina.7 The sympathetic denervation of the heart provided a reasonable result in terms of diminishing the symptoms of angina, and was also thought to produce coronary vasodilatation. This procedure was carried out fairly widely for a number of decades. Surgeons differed as to how the procedure should be performed and how extensive it should be. The Jonnesco-type sympathectomy was criticized by Danielopolu (Director of the Second Medical Clinic at the University of Bucharest) on the grounds that it produced an irreversible deterioration in cardiac function. He therefore directed his surgical colleague, Hristide, to cut the posterior roots of the upper thoracic spinal nerves, thereby dividing only the sensory fibres. Danielopolu later declared cervicothoracic sympathectomy to be disastrous from a therapeutic point of view, and concluded that the removal of the stellate ganglion was incompatible with life.

Several other techniques of cardiac denervation emerged in this period including paravertebral alcohol injection (destruction of the upper thoracic sympathetic ganglion by alcohol injection), posterior rhizotomy (section of the upper five thoracic posterior nerve-roots on both sides), ganglionectomy (removal of


of the inferior cervical and upper three thoracic sympathetic ganglion)\(^8\) and cardiac irradiation.\(^9\) The extensive operation and lack of complete relief from angina made them somewhat questionable in patients with significant coronary artery disease.

**Thyroidectomy**

The premise behind use of thyroidectomy for the treatment of angina was that it reduced the cardiac workload by lowering the metabolic rate so that the demands on the myocardium are reduced. It had been observed that some patients developed congestive heart failure or angina when the classic signs of exophthalmic goiter appeared, and that their cardiac symptoms occasionally improved after remission from thyrotoxicosis. In 1926, Boas performed the first subtotal thyroidectomy on a patient with angina. Unfortunately, it was not successful.\(^10\) Later, Blumgart observed temporary improvement of cardiac symptoms when patients with no evidence of thyroid toxicity were subjected to subtotal thyroidectomy, consequently total thyroidectomy was recommended.\(^11\) Harold Rosenblum and Levine reported a reduction in congestive heart failure and angina in hyperthyroid patients following thyroidectomy arguing that the result obtained in one patient whose thyroid was found to be normal suggested that this procedure might prove useful in the treatment of a variety of heart disorders.\(^12\)

The first total thyroidectomy in such patients was performed by Elliott Cutler on

\(^8\) White, Smithwick and Simeone. The autonomic nervous system 1952.


\(^12\) Rosenblum and Levine. Am J Med Sc 1933; 185:219-33.
December 14, 1932. He also performed subtotal thyroidectomies in several patients in order to relieve angina, and found that their symptoms improved. However, while it provided symptomatic relief in 80% of patients, it often resulted in them being transformed physiologically and psychologically into a vegetative state. Eventually, the operation was modified to only a simple ligation of the superior and inferior thyroid arteries. Some authorities declared that improvement was not maintained. In 1947, Bourne stated that total thyroidectomy was still the best method of decreasing the motor activity of the heart. Patients were obtained relief for five years after the operation. As the mortality was as high as 9% and improvement was not necessarily maintained, White, Smithwick and Simeone in 1952 considered the operation to be unjustifiable for treatment of cardiac pain. The development of antithyroid drugs and radioactive iodine was a valuable adjunct to the treatment of cardiac pain without the risk of surgery. In 1948, Blumgart reported using iatrogenically induced hypothyroidism employing radioactive iodine for the treatment of angina. This was effective in about 50% of cases. By this time, the induction of hypothyroidism had fallen into disrepute and the results of various operative efforts to increase myocardial circulation were judged to be promising.

**Indirect Coronary Revascularization**

**Pericardectomy, pericardial abrasion, cardiopericardiopexy, cardiomyopexy**

In 1930, Claude Beck championed early attempts at increasing the blood supply to the myocardium by inducing pericardial scarring and thereby encouraging neovascularization. Support for this approach came from the

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15 White, Smithwick and Simeone. The autonomic nervous system 1952.

research of AR Moritz who in 1932, injected carbon particles into the coronary arteries of cadaver hearts and analyzed the extensive network of collaterals between vascular territories, as well as the vascularization of pericardial adhesions. Moritz also noted the enhanced anastomoses between the coronary arteries and extracardiac structures in humans dying of pericarditis, as well as the vascular anastomoses between pericardial fat pads and branches of the aorta. Beginning in 1932 with animals and in 1935 with human experiments, Beck developed two procedures, namely cardiopericardiopexy or pericardial poudrage and cardiomyopexy. The first procedure involved inducing pericarditis by mechanical abrasion to the epicardium. The second operation consisted of epicardial abrasion, inducing pericarditis by instillation of powdered bone into the pericardial space (poudrage) and suturing a pectoralis major muscle graft (cardiomyopexy) onto the epicardium. He performed a cardiomyopexy on a patient on February 13, 1935, the first such operation in a human. The patient had no angina seven months after the operation. By 1936 Beck reported that six of eleven very ill patients so treated were living. The latter procedure lead to the search for ever-better means of inducing vascular pericardial adhesion by chemical irritants such as sodium morrhuate, sand, and talc, as well as the search for appropriate vascular organs to contact with the abraded epicardium. British surgeon, Laurence O’Shaughnesssy performed the first cardioomentopexy on


October 2, 1936. He also performed cardiopneumopexy in August 1937. He reported in the summary that all fourteen survivors were better for six months or more, that those who had been bedridden were walking about, and that those who had been unable to work had returned to work. There was only one fatality.22 Several other operations (cardiojejunoopexy, cardiogastropexy, cardiolienopexy) and revascularization of the heart by tubed pedicle graft of skin and subcutaneous tissue were also developed.23

**Redirect of venous drainage of the heart**

In 1934, Robertson while experimenting on dogs, ligated the great cardiac vein. This procedure raised the venous pressure and redirected the blood flow in thebesian vessels from the chambers back into the myocardium. Louis Gross in 1936 at Mt. Sinai Hospital in New York demonstrated the benefit of partial coronary sinus ligation in dogs who had been subjected to ligation of the anterior descending coronary artery. Compared with a control group these dogs showed a decreased rate of infarction and increased survival.24 On April 14, 1939 Mercier Fauteux of Montreal first used Gross’ technique of great cardiac vein ligation on a human subject. The outcome was positive with the patient being free from angina for two years.25 Five additional patients were treated similarly. Fauteux and his group also experimented with pericoronary neurectomy and reported good results.

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combining coronary vein ligation with pericoronary neurectomy. However, great cardiac vein ligation was discontinued after extensive experimental study. Robert and colleagues in 1943 carried out the first experimental coronary sinus arterialization using brachiocephalic, subclavian, and innominate arterial grafts placed through glass tubes. In 1953, Bailey and colleagues reported their and Dr Claude Beck’s experience of coronary sinus arterialization using the jugular vein, anastomosed between the descending aorta and coronary sinus, and proximal partial occlusion of the coronary sinus in 18 patients. The anastomosis could not be performed in two patients, and the operative mortality rate was 11.1%, with one patient having empyema thoracis, two having thrombosed anastomosis, one dying six months after surgery, and another four with graft thrombosis. Only seven patients improved their symptoms.

Although Beck had initially concluded that coronary sinus ligation was not justified for clinical use, by 1954 he was employing it routinely along with pericardial poudrage and mediastinal grafting. This triple tiered technique became known as the Beck I operation. Results of the Beck I procedure were reported in 1955. In summary, 90% of patients had a definite improvement in angina and half had no residual angina at all; 90% returned to work, with 35% of all patients having no work limitation and 55% having some limitation; and the mortality rate of 6.6% was attributed primarily to the severity of the underlying disease.


Beck procedure continued to be used by Beck and many other cardiac surgeons, and, with modifications became the most common operation for coronary disease until the era of aortocoronary bypass surgery. In 1946, Beck also began to experiment with coronary sinus arterialization in dogs using either common carotid or intercostal arteries, or a free autologous jugular vein graft. In January 1948 he commenced using this technique clinically. The operation involved the interposition of an autogenous systemic arterial graft between the descending thoracic aorta and the coronary sinus, and operative constriction of the coronary sinus a few weeks afterwards. This procedure became known as the Beck II operation, which involved a staged procedure consisting of coronary sinus arterialization followed by partial sinus ligation. However, due to the invasiveness of the procedure it was not widely used.\(^{32}\)

**Increasing left heart volume**

In 1939, Lillehei created a surgical communication between the pulmonary artery and left atrium in patients in an effort to increase left heart volume and thus antegrade coronary artery blood flow. However, this right to left shunt caused major physiological problems and thus was not suitable for clinical use.\(^{33}\)

**Increasing coronary collaterals**

Also in 1939, Fieschi suggested that the bilateral ligation of the distal internal thoracic arteries would shunt flow through branches of the pericardiophrenic arteries back through the heart via vascular anastomoses within the epicardium.\(^{34}\) Fieschi and colleagues reported their results in 1942. Battezzati and colleagues reintroduced this procedure in 1955. Few surgeons however were

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\(^{34}\) Fieschi.  Arch Ital Chir 1942; 63:305-310.
convinced that this was a rational approach to the problem.\textsuperscript{35} It was shown that ligation of such small vessels did not affect the arterial pressure in the vessels proximal to the obstruction indicating that the concept was flawed.

**Increasing pulmonary collaterals**

In 1956, Kline and associates occluded the left pulmonary artery in dogs in order to increase the bronchial artery collateral flow. He then sutured parts of the lung to epicardium denuded by silver nitrate.\textsuperscript{36} In 1957, Kownacki increased pulmonary collateral flow to the heart by ligating the lingular vein and then suturing the lingula to the epicardium.\textsuperscript{37} Unfortunately, the increasing myocardial supply through such collaterals was minimal.

**Transmyocardial revascularization**

The concept of transmyocardial revascularization was based on knowledge of the myocardial sinusoids and the thebesian system. Goldman and colleagues in 1955 made a tunnel in the myocardium using a carotid arterial graft (U shape or straight graft) and a polyethylene tube in order to direct blood from the heart chamber to the myocardium in dogs. After ligating the anterior descending artery, significant reductions in the number of myocardial infarctions as well as improved survival rates were reported.\textsuperscript{38} Massimo and Boffi in 1956 used a T-shaped polyethylene tube, 4 mm in diameter, inserted in such a way that the horizontal branch was imbedded inside the ventricular wall (subendocardial layer) with the vertical branch opened to the ventricle. Favorable results were produced using this


\textsuperscript{36} Kline, Stearn, Bloomer and Leibow. Am J Pathol 1956; 32:663-693.


technique. Sen and colleagues, in 1965, tried to recreate the reptilian myocardial vascular pattern in the mammalian animal. They simply acupunctured the myocardium and demonstrated a reduction in infarction size and an increased survival rate. However this concept of direct myocardial revascularization from the ventricle was criticized by surgeons who argued that flow from the ventricular cavity to the myocardium during systolic contraction was impossible. Although the development of coronary artery surgery resulted in a decline in interest in indirect coronary revascularization, there has recently been a return to microcirculatory approaches for the treatment of ischemic heart disease with a number of surgical teams using lasers to produce multiple small sinusoids in the myocardium. Mirhoseini and colleagues conducted a series of animal experiments using lasers to create tunnels in the myocardium. Subsequently, transmyocardial laser was clinically employed in 1983. Gene therapy has also been used as an adjunct to transmyocardial laser therapy in order to increase angiogenesis. While there have been some promising initial results, the mechanism by which transmyocardial laser revascularization works is not understood and there is


considerable debate over which aspects of the process are responsible for the clinical effects that have been measured.\textsuperscript{45}

**Direct Coronary Revascularization**

The idea of operating directly on the coronary arteries was conceived as early as the first decade of the twentieth century when Alexis Carrel’s experiments grafting both arteries and veins in animals paved the way for the development of direct coronary artery bypass grafting in humans. He developed a technique of vascular anastomosis (applicable to either small or large arteries and veins) which achieved a watertight suture without narrowing the caliber of the vessel.\textsuperscript{46} His experimental results of anastomosing the innominate artery of one dog into the distal coronary artery of another were reported in 1910. He also performed the first coronary artery bypass using a free carotid artery graft.


\textsuperscript{46} Carrel. Lyon Med 1902; 98:850.
anastomosed between the descending thoracic aorta and left coronary artery.\textsuperscript{47} In addition, he first performed vein bypass grafting by anastomosing a vein into a transected aorta.\textsuperscript{48} At this time, this operation was performed with difficulty and carried a high mortality rate. In 1912, Carrel was awarded the Nobel Prize in Medicine or Physiology for his work on transplantation and vascular grafting.

The first report of direct implantation of vessels into the myocardium of a human was by Griffith and Bates in 1938. They repaired an accidentally perforated left ventricle with pectoral muscle and sutured the branches of the internal thoracic artery into the myocardium.

The idea of direct coronary revascularization was also included the endarterectomy technique which was expanded after successful endarterectomy for the occlusive disease of the abdominal aorta and its branches. Abosolon and colleagues and May performed experimental endarterectomy in dogs.\textsuperscript{49} The first successful coronary artery endarterectomy in human was performed by Bailey and colleagues on Oct 26, 1956 without cardiopulmonary bypass.\textsuperscript{50} The coronary endarterectomy had been used in several centres for a period of time.\textsuperscript{51} Nevertheless, the mortality rate was high, due mainly to dissection of the distal


\textsuperscript{50} Bailey, May and Lemon. JAMA 1957; 164:641-646.

portion of the coronary artery or occlusion of important side branches, and procedure was used less frequent.\textsuperscript{52}

**Venous conduits**

It was not until 1940, however, that Carrel’s ideas were developed further when the Canadian surgeon, Gordon Murray, began experimenting with direct coronary artery anastomoses, including the use of venous interposition homografts using sutures.\textsuperscript{53} A major development during this period was the prevention of clotting and thrombosis of the graft by the anticoagulant “heparin”, research pioneered by Murray.\textsuperscript{54} The technique of repair of blood vessels, grafts in blood vessels, and surgery of blood vessels was developed by Carrel during the period of the First World War and shortly afterwards, however success was minimal due to the incidence of clotting and thrombosis, which formed the need for an anticoagulant. A number of important surgeons had tried with some success, to alleviate cases where gangrene was inevitable as the result of plugging of great blood vessels by thrombus. Dr. Einer Key of Sweden, Dr. Meyer and Dr. Trendelenburg in Germany, Dr. Evarts Graham in America and others approached this subject with great boldness and performed feats in vascular surgery which were previously unknown at that time. Many attempts were made to prevent clotting. Key along with others advocated the use of sodium citrate. However, due to its toxicity, it could only be used during operations in the operative field and could not be administered systemically, which posed a perplexing and fundamental problem.

\textsuperscript{52} Favaloro. Circulation 1972; 46:1197-207.


\textsuperscript{54} Murray. Medicine in the Making 1960.
Hirudin, extracted from the leech, was recognized as the most effective anticoagulant. It was applied to the affected area in patients. Attempts were made to introduce it beneath the skin, but the substance was so toxic that it was not suitable for this form of application. Searching for a more effective method, Murray learned of a substance, heparin, originally an extract of liver (hepar = liver), which had been discovered in Professor Howell’s laboratory in Philadelphia. Heparin was reported to work well as an anticoagulant, but was noted for its toxicity to animals, and therefore had not been used on humans. Murray continued with his investigation believing that heparin toxicity may be due to impurities. He did not receive support from his colleagues and indeed many senior surgeons objected to his research interests. To overcome these objections, he had to undertake research during his “off-duty” hours and at night.

Murray firstly studied the process of blood clotting under the microscope by mixing blood with a small quantity of heparin solution. The blood on the slide remained dispersed. The cells did not agglutinate into clumps and there were no visible changes in arrangement. He showed that the substance neutralized a prothrombin, thus making it an antiprothrombin. This prevented the protein part of the blood, fibrinogen, from forming a solid matrix. His experiments showed that heparin had this effect in animals, but toxicity still existed. Control experiments were performed for comparison, so that the effect of giving heparin under standard conditions could be observed. Simultaneously, purification of the substance was being conducted by the Chemistry section of the Department of Physiology. Murray determined the dosage necessary to get the required effect experimentally and clinically. He performed many experiments to study a delivery method, the maintenance level and the necessary duration of administration of heparin. He then performed a simple division across a fairly large artery, such as the carotid artery and immediately sutured it. This produced a roughened and damaged area in the vessel which, if left to itself would have become plugged with thrombus. On the injection of heparin, however, the clotting was prevented and the vessel healed perfectly and within about three days further heparin was unnecessary.
Following this, Murray engaged in work which was to be of great significance in its application to clinical surgery. A portion of an artery was removed and the gap was bridged by grafting a piece of vein from an animal. His sceptical colleagues on the hospital staff considered this concept ridiculous, stating that no vein could withstand arterial blood pressure and that obviously the experiment could not succeed. This particular experiment had been performed by French surgeons in the 1880’s, but all such grafts had failed because of plugging with thrombus. Now, with the use of heparin, which was becoming more purified with the diligence and efforts of the chemists, these vessels were kept patent so that what had never been possible before, was now accomplished. Observations were made of changes in the vein under arterial pressure. Changes such as those occurring during healing were studied at short intervals and continued until the vessel was restored to a normal functioning structure, replacing the original artery. It was upon these experiments and their results, made possible by the use of heparin that the subsequent popularity of vascular surgery was to rest, as was its wide application in a great variety of human injuries and diseases including the repair of many congenital defects in the vessels, repair of degenerated conditions in vessels, even in the aorta, and in cerebral and coronary arteries. Murray was invited on many occasions to address the leading national and international surgical bodies in the United States. He was also invited to give the Hunterian Lecture in 1939 before the Royal College of Surgeons in London, England. He also introduced the “direct attack” concept on another process occurring in the blood — thrombosis — against which it was not known whether heparin was effective. At intervals he received some technical assistance through the Department of Surgery, but his own work was undertaken without remuneration and his own funds went into expenses involved in the experimental work. In the meantime the chemists, Drs. Charles and Scott, had worked valiantly to produce the improved heparin. The expense soon became a burden on the department. Mr. J. S. MacLean, a close friend, had watched with much interest the various experimental problems resolved, and generously provided funds to cover the further expenses.

Murray had already received an intravenous injection of a small dose of
heparin without ill effects, so it was decided to use it clinically. The toxic effects of heparin in humans were still evident in the early stages of research, however they were soon eliminated. Heparin began to be used clinically for pulmonary embolism, thrombophlebitis and coronary thrombosis. Murray also performed end-to-end suture of severely injured vessels at the elbow region in a car accident patient as well as performing the first successful graft placed in the arterial system of a human being. The patient was a newspaper boy who had inadvertently driven a knife into his groin region, dividing the main femoral artery. He had collapsed, whilst in the hospital, a surgeon exposed the area and tied off both ends of this great vessel according to the orthodox method at the time. This stopped the hemorrhage but within a few hours it became evident that while the patient was stable, the circulation to the leg was inadequate. Dr. Burns Plewes, who had performed the operation, was aware of Dr. Murray’s experimental work, and with great resolve removed the patient from his own hospital and rushed him to the General Hospital. Murray was unable to get the two ends of vessels together without tension therefore he dissected out a vein in the region of the operative field, removing a length sufficient to bridge the gap in the main artery. As the venous system has a series of valves at short intervals, the graft had to be turned end to end, so that the valves would stay open and not impede the circulation. He grafted the vein by suturing the two ends of the divided artery, bridging a gap of about two and a half inches. After injecting heparin solution the circulation was restored. The patient made an excellent recovery with normal circulation in the extremity, and under observation for many years everything continued to be normal. There were to be further improvements in the grafting of vessels. It was demonstrated, for example, that a portion of an artery would work as well as a vein graft in some conditions, and better in others. In subsequent years vascular surgery progressed steadily, until the aorta itself was being operated upon, most commonly for aneurysm. His first, and one of the earliest in the abdominal aorta was a homologous graft of aorta removed at postmortem. Subsequently, many grafts were performed and eventually this type of surgery spread to all the large medical centres. All of this success in surgery depended on the development of his anticoagulant.
Gordon Murray also was interested in heart disease. During early year of his practice, hearing of the activity in surgical treatment of heart disease in Cleveland, he visited Dr. Elliott Cutler and his assistant at that time, Dr. Claude Beck. Dr. Cutler, later Professor of Surgery at Harvard, was working on the problem of mitral stenosis which was one of the commonest forms of acquired heart disease. He was also working with a large group of patients suffering from coronary heart disease. It is curious to think that before 1912, when Herrick of Chicago described coronary disease, such a diagnosis had never been made.

In the 1950s cardiopulmonary bypass techniques were developed that paved the way for the more precise techniques later performed on the nonbeating heart. In this same period the systemic hypothermia technique was developed. In 1953 Gibbon perfected the first effective heart-lung bypass machine, using a screen oxygenator. In 1959, Dubost and colleagues became the first to perform a coronary operation in a human using cardiopulmonary bypass when they carried out a coronary ostial reconstruction on a patient with syphilitic aortitis. An effective heart-lung bypass was available by the mid-1950s, but would not be used routinely in operations for ischemic heart disease until the late 1960s. Another landmark event in coronary surgery was the development of coronary angiography by Sones and colleagues, who in 1958 conducted the first selective injection of contrast media into coronary arteries. This development allowed for precise definition of anatomic obstruction and laid the foundation for direct bypass surgery.


Reverse saphenous vein grafting techniques from the ascending aorta to a coronary artery were first tried in an animal experiment by DeBakey and Henley in 1961. These grafts functioned in 50% of dogs. The saphenous vein was first used in a human for coronary artery bypass grafting by David Sabiston, Jr, on April 4, 1962 at Johns Hopkins. The patient however suffered a stroke two days after surgery and died, and this was not published until 1974. The world’s second human vein bypass graft operation, and the first successful one, was performed by Garrett, Dennis and DeBakey at Methodist Hospital in Houston on November 23, 1964, on a 42-year-old man. The vein graft to the left anterior descending artery remained patent for seven years after surgery. Unfortunately, the patient died the following year from an occlusion in the grafted vessel distal to the insertion of the patent vein graft. This was not reported until 1973. In 1967, Rene Favaloro popularized the use of the saphenous vein as an autologous vein conduit. Initially, the saphenous vein was employed using an end-to-end distal anastomosis, with the proximal end of the right coronary artery ligated. Later, Favaloro and his team performed vein bypass grafting with an end-to-side distal anastomosis with the proximal end sutured to the ascending aorta. This became the standard coronary artery operation. Johnson in Milwaukee also deserves credit for early use of the saphenous vein. In 1969 he reported to the American Surgical Association a mortality rate of 2% on the left coronary artery bypass operation in 301 patients. Consequently, the vein bypass procedure became the standard operation throughout the world. Between 1967 and 1971, Favaloro and his colleagues at the Cleveland Clinic performed 3,185 saphenous vein grafts in 2,201 patients.


60 Garrett, Dennis and DeBakey. JAMA 1973; 223:792-94.


While the saphenous vein was the primary vessel used for grafting, surgeons also experimented with a number of other venous conduits. In 1969, Kakkar reported the first use of an arm vein for grafting. 63 Cephalic veins were used as bypass grafts in seven patients with arterial disease of the lower extremity, and all were found to be patent with no dilatation of the graft after 4-12 months. Schulman and Badhay used 68 arm veins in femoropopliteal grafting and reported in 1982 that most of the conduits rapidly developed intimal hyperplasia and occluded. 64 The few that were still patent had elongated and had become aneurysmal. Jarvinen and colleagues, in 1984, reported their experiences with the arm veins as aortocoronary bypass grafts in 15 patients. A total of 34 anastomoses were performed with 16 arm vein grafts and they found a patency rate of 87% at mean follow-up of 1.4 years. 65 Stoney and colleagues reported in 1984 arm vein graft patency of only 57% at 2 years follow-up by angiography in 28 of 59 patients. 66 The probable reason for the poor performance of the arm vein as a graft is that the velocity of blood flow from the upper extremity is approximately one-half that of the lower extremity flow, and that arm veins have only one half the tensile strength of leg veins. Thus, powerful arterial hemodynamic forces, along with the degradation of wall elastin, cause the vein to elongate and become tortuous and aneurysmal soon after implantation. 67 This is associated with a low flow velocity and predisposition to atherosclerosis. Consequently, reports of suboptimal results from use of arm veins in comparison with those of internal


thoracic artery and saphenous vein grafts led to the abandonment of the arm vein as a bypass graft.

In 1975, Crosby and Carver reported using the lesser saphenous vein as an alternative venous conduit for aortocoronary bypass in three patients. Following Crosby’s report, other researches also experimented with using the lesser saphenous vein. However, these studies were limited by small patient samples and lacked long-term follow-up. While patency of the lesser saphenous vein theoretically should have been similar to that of the great saphenous vein, the small numbers of patients receiving lesser saphenous graft made it hard to draw conclusions.

In 1974, three large clinical trials: Veterans Administrative (VA) Cooperative Study (1972-1974), European Coronary Surgery Survey (ECSS) (1973-1976) and Coronary Artery Surgery Survey (CASS) (1975-1979), were initiated comparing surgical versus medical treatment of ischemic heart disease. The VA study demonstrated improved survival only for patients with significant left main artery disease. Survival in the high-risk subgroup was 87% for the surgically treated patients and 74% for those treated medically, a highly significant difference after four years of follow-up. However, exclusion of the left main artery disease group reduced the difference to a non-significant (84% for surgery versus 79% for medical treatment) result. Among patients not in the high-risk subgroup, survival at four years (with left main artery excluded) was 93% for those treated surgically and 96% for those treated medically. For all patients, the

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rates were 85% and 86% respectively.\textsuperscript{71} The surgical advantage for patients with impaired left ventricular ejection fraction was significant at 5 years ($P = 0.03$) and 8 years ($P = 0.05$) but appeared to have diminished at 10 years ($P = 0.15$).\textsuperscript{72} The benefits of CABG on survival, symptom control and postinfarction mortality were transient and lasted less than 11 years. The benefits began to diminish after 5 years, when graft closure accelerated.\textsuperscript{73} The overall 22-year cumulative survival rates were 25% and 20% in the medical and surgical cohorts ($P = 0.24$).\textsuperscript{74}

The ECSS study demonstrated a significantly higher survival rate ($P = 0.0001$) in the surgical group (92.4±2.7%) than in the medical group (83.1±3.9%) at the 5 years follow-up interval. However, during the subsequent seven years, the survival rate in the surgical group decreased more rapidly.\textsuperscript{75}

In the CASS study, CABG benefited patients with left main coronary artery disease or left main equivalent (combined proximal LAD and proximal left circumflex artery), patients with poor left ventricular function and patients with normal left ventricular function with at least 1.00 mm of ischemic ST-segment depression or low exercise capacity.\textsuperscript{76} The indexes of quality of life such as

\begin{footnotesize}
\begin{itemize}
\item \textsuperscript{72} Scott, Deupree, Sharma and Luchi. Circulation 1994; 90:II120-3.
\item \textsuperscript{73} The VA Coronary Artery Bypass Surgery Group. Circulation 1992; 86:121-30.
\item \textsuperscript{74} Peduzzi, Kamina and Detre. Am J Cardiol 1998; 81:1393-9.
\end{itemize}
\end{footnotesize}
angina relief, increased activity and reduction in use of anginal medications initially appeared superior in patients assigned to surgery than medical treatment, however by 10 years these advantages were much less apparent. 77 The significance of the CASS study was hampered by the fact that (1) the CASS randomized study applied to only a small minority of patients with coronary artery disease 78; (2) 37% of the medical group had undergone CABG because of increasing chest pain during 10 years follow-up which created a bias against surgical treatment. 79

Thus, while these studies showed encouraging results, at least in the short term, overall they supported the use of surgical revascularization for coronary artery disease. 80 These early series mostly employed saphenous vein grafting.

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later became apparent that one of important risk factors for death and postoperative angina was the use of only vein graft.\textsuperscript{81}

**Arterial conduits**

### Internal Thoracic Artery

In 1945, Vineberg developed a technique subsequently known as the Vineberg procedure.\textsuperscript{82} This involved implanting the internal thoracic artery (ITA) and other vessels into the myocardium in order to augment its blood supply. While this technique should be included in the indirect vascularization category, it was an important precursor to CABG as it was the first time the ITA had been used to revascularize the myocardium. Vineberg and Miller implanted the distal end of ITA into a myocardial tunnel (5 cm) in the anterolateral wall of the left ventricle between the left anterior descending artery and the circumflex coronary artery to create new coronary collaterals.\textsuperscript{83} They cut the sixth intercostal branches to permit side flow and pulling the ITA through the tunnel and fixing it at its distal end. Some year later, it was shown collaterals developed between the ITA and coronary artery. The ITA was also patent as long as 17 years later.\textsuperscript{84} More than 5,000 of these operations were performed between 1950 and 1970, with at least subjective improvement of angina in many patients. Vineberg also described the use of the right gastroepiploic artery for his operation if the ITA was not suitable.

In 1957, Smith and colleagues modified the Vineberg procedure. They used the saphenous vein and nylon tubes anastomosed to the descending aorta, made

\textsuperscript{81} Cameron, Davis and Rogers. J Am Coll Cardiol 1995; 26:895-9.


\textsuperscript{83} Vineberg and Miller. Surg Forum 1950; 5:294-299.

\textsuperscript{84} Vineberg. JAMA 1975; 234:693-694.
multiple holes in the graft and then placed into the myocardial tunnel.\textsuperscript{85} Sabiston, Fauteux and Blalock used the carotid artery as a modified Vineberg procedure.\textsuperscript{86}

In 1954, Murray reported the successful experimental use of arterial conduits (axillary or carotid arteries) placed from ascending aorta to the coronary arteries by direct anastomosis in five dogs.\textsuperscript{87} Murray was interested in the fact that the heart lies in its pericardial cavity unattached to anything except through the narrow pedicle at its base, at which point the great vessels enter and leave. He began experiments trying to reproduce the conditions that in theory might augment circulation to the heart. In animals, grafts of surrounding vascular tissue carrying a good supply were stitched on to the heart in various positions. The effects of the grafts were tested, after varying lengths of time, by the original coronary arteries being tied off one at the time in order to see if the grafts were supplying sufficient nutrition to the heart. Using this procedure on an animal, he was able to create sufficient circulation to the heart from other sources. He commented, “the ITA, which runs over the top of the heart, seems particularly suitable for the source of such grafts”. A portion of the muscle in which the ITA ran, and even the bare artery itself, was transplanted into the wall of the heart, in the hope of giving it increased circulation. In addition, foreign bodies were placed in the sac around the heart, in expectation that they might provide a vascular source through adhesions, which would improve cardiac circulation. In years to come many of these techniques were perfected, and have been used clinically resulting in considerable improvement in patient outcomes.

However, the first successful anastomosis of the ITA to the left anterior descending (LAD) was performed in 1953 by Russian surgeon, Vladimir P.


Demikhov in animals. Robert H. Goetz performed the first successful human CABG, on May 2, 1960, anastomosing the right ITA to the right coronary artery using a tantalum ring. An angiogram at 14 days postoperatively demonstrated a patent anastomosis and the patient remained free of angina pectoris for one year. Demikhov’s experimental work paved the way for the work of another prominent Russian surgeon, Vasilii I. Kolessov who, in 1964, performed the first sutured ITA to coronary artery anastomosis in a human subject.

In 1968 a number of surgical teams began performing ITA grafting. However, despite occasional reports of successful ITA-to-LAD grafting, from the early seventies to the eighties, the saphenous vein was, for the most part, the conduit of choice for CABG. The ITA was used in less than 15% of coronary artery bypass procedures as late as 1981. The main reasons for this situation were: (1) the abundant supply of veins; (2) the fact that the saphenous vein is easy to harvest and suture; and (3) the superior flow rates of the saphenous vein compared to the ITA.

During the 1980s, there was a shift to arterial revascularization due to an increasing awareness of the problems involved with long-term vein graft patency and an accumulation of data demonstrating the excellent patency rates of ITA.


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grafts. The occlusion rate of the saphenous vein was 12-20% in the first year. The occlusion rate was 2-4% during the first 4-5 years while the yearly occlusion rates doubled to 4-8% between 5 and 10 years. Approximately 50% of saphenous veins were occluded at 10 years. These results clearly demonstrated a higher failure rate than those of the ITA. In 1983, Campeau and colleagues found that only 30% of vein grafts were in a satisfactory condition 10 years postoperatively. Meanwhile, Okies and associates found that the 10-year survival and patency rates were significantly better in those patients who had received an ITA rather than only saphenous vein grafts. In 1986, Loop and associates reported better survival rates for patients who had received both ITA grafts and saphenous vein grafts than those who were given vein grafts only. More recently, a number of studies also have shown that, compared with vein grafts, ITA grafting to the LAD results in a better survival rate, less recurrent angina, and a higher long term graft patency. While previously being used only


95 Bourassa, Campeau, Lesperance and Solymoss. Cardiology 1986; 73:259-68, Campeau,
Enjalbert, Lesperance and Bourassa. Canadian Journal of Surgery 1985; 28:496-8, Campeau,


98 Cameron, Davis, Green, Myers and Pettinger. Circulation 1988; 77:815-9, Lytle, Loop,
in younger patients, complete arterial grafting is now used in patients of all ages with most surgeons now viewing arterial bypasses, in particular single left internal thoracic arteries, as the graft of choice especially when attached to the left anterior descending coronary artery.

In studies of long-term graft patency, the ITA, when compared with saphenous vein grafts, has been demonstrated to be the far superior conduit for coronary artery bypass surgery. At 10 years, ITA grafts have been shown to have up to 90% patency, in comparison to vein grafts with 25-50% patency. The lower percentage in veins is largely explained by the fact that saphenous vein grafts tend to develop late postoperative atherosclerosis while internal thoracic arteries remain relatively free of disease.

These facts, along with the increased number of repeat coronary bypass procedures being performed, and the limited availability of the ITA, have resulted in a number of surgeons experimenting with the use of other arteries for coronary artery bypass grafting.

**Radial artery**

The RA initially was used as a conduit for coronary artery bypass grafting by Carpentier and associates in 1973. In contrast to other arterial conduits, the RA appeared to offer a highly promising alternative for a number of technical reasons. It is similar in length and size to the internal thoracic artery, its diameter is closer to the size of the coronary artery than that of the saphenous vein graft, it is easily harvested, and rarely affected by atherosclerosis. However, despite these potential advantages, Curtis and colleagues reported in 1975 that the failure rate of RA grafts in a group of 79 patients was 64.7% at 6 to 12 months after operation. This represented a significantly higher failure rate than that of the

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saphenous vein and ITA grafts used in the same patients. Furthermore, one of the histologically normal RA grafts removed at reoperation revealed marked concentric intimal hyperplasia. This shed considerable doubt upon the viability of the RA as an alternative graft. In 1976 Chiu suggested that the thick-walled RA appeared to depend more on vasa vasorum for its integrity than the thin-walled vein. The vasa vasorum of free RA graft, which disrupted at both ends, cannot regenerate readily from the adjacent tissue and may have been more vulnerable to intimal hyperplasia and occlusion than either vein grafts or ITA grafts. In 1976 Fisk and colleagues reported results from 48 RA grafts. After 1 to 24 weeks, only 50% of RA grafts were patent compared with 77% of saphenous vein grafts. These authors suggested that the RA should not be used. As a result of these poor results the RA fell out of favor, and only recently has been rediscovered as a viable conduit.

The early 1990s witnessed a revival of interest in the RA. During this period, Carpentier and associates were contacted by a patient who had been part of their trial conducted in the 1970s. This patient’s RA graft was thought to have occluded soon after surgery. However, to their surprise, an angiogram 18 years later indicated that the RA was in fact patent and free from disease. This discovery led to Acar and colleagues to reinvestigate the use of the RA for CABG.

**Other Arterial Conduits**

Over the past decade or so, surgeons have experimented with other arterial conduits such as the right gastroepiploic artery and the inferior epigastric artery. In 1987 Pym, Suma, Attum and Carter reported using the right gastroepiploic

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artery (RGEA) as a bypass conduit. Anatomical Studies demonstrated the constant presence of a direct intramural anastomotic circulation between the right and left gastroepiploic arteries and showed that size of the RGEA was appropriate for grafting. Histopathologic studies showed mild intimal hyperplasia in the RGEA. Immunocytocchemical and ultrastructural examination revealed similarity of smooth muscle and endothelial cells in the gastroepiploic artery and the ITA. Although there are differences in vasoreactivity between the RGEA and ITA, the gastroepiploic artery is now an established alternative to the ITA. Although little is known about its long-term patency, studies have shown that it has an excellent short to mid-term patency. In Suma’s series the early


patency rate of the RGEA was 94% (253/268) and the late (2-5 years) patency was 94% (47/50). In 1994, Grandjean and colleagues reported the results of the RGEA in combination with one or both ITAs in 300 patients.\textsuperscript{111} Hospital mortality was 3.3%. Two of these patients had an infarct in the area revascularized by the gastroepiploic artery. There were no deaths at mean follow-up of 14 months (0.5 to 39 months). One patient with an occluded RGEA graft underwent reoperation using right ITA. The other had percutaneous transluminal coronary angioplasty of the right coronary artery after occlusion of the RGEA. Elective recatheterisation was performed in 88 patients at 1 to 25 months after operation (mean 10 months). Patency in RGEA grafts increased steadily from 77% in the first semester of the study to 95% in the fourth semester which then equaled the patency of the ITA grafts (97%), which was constant. In 1995, Bergsma and colleagues reported the results of arterial grafting using RGEA and bilateral ITAs in 256 patients.\textsuperscript{112} Seven-year actuarial survival was 91.1%. The cumulative probability of event-free survival for myocardial infarction, re-intervention and angina pectoris at 7 years was 97.3%, 95.4%, and 85.4%, respectively. They also found 85.4% freedom from angina pectoris after 7 years, which is lower than the results of studies in which vein grafts, single ITA grafts or double ITA grafts were used. In 1995, Jegaden and colleagues reported the results of use of the RGEA grafting to bypass the right coronary artery trunk or branches in 400 patients.


(mean age 59 ± 9 years). The RGEA was used alone in six patients, associated with one ITA in 111 patients (two arterial grafts, 2.2 ± 0.4 anastomoses) and with both ITAs in 283 patients (three arterial grafts, 3.4 ± 0.6 anastomoses). No vein graft was used. Early (15th postoperative day) angiographic study of the RGEA graft was performed in 104 patients; the patency rate was 92%. Anomalies of RGEA grafts were three occlusions, five stenoses, three with competitive flow and none had a string or slender sign. The 2- and 4-year actuarial survival rate was 96.7 ± 1.9%. The rate of late cardiac events was 2% patient/year; angioplasty for right gastroepiploic graft failure was required in four patients. In 1996, Voutilainen and colleagues reported a 5-year angiographic follow-up study of RGEA grafts in 31 consecutive patients who underwent coronary artery surgery between March 1987 and May 1990. The 5-year patency of RGEA grafts was 82.1% with a 95% confidence interval of 63.1% to 93.9%. The 5-year patency of the left ITA was 90.3% and for the right ITA 94.4%. This result was superior to the 66.7% patency of venous grafts. In 2000, Suma reported that the cumulative patency rate of RGEA graft, estimated by the Kaplan-Meier method, was 96.6% at 1 month, 91.4% at 1 year, 80.5% at 5 years, and 62.5% at 10 years. Although acceptable results for the RGEA have been reported, there are severe complications and morbidity directly related to use of this graft: coronary artery steal syndrome, pancreatitis, gastric perforation, splenic injury requiring splenectomy, diaphragmatic hernia and intraabdominal abscess.


The inferior epigastric artery was first used by Puig in 1990. Its role as an arterial alternative has been less popular however because it tends to become narrower at its distal end, does not always yield an adequate length of viable conduit, and is extremely muscular and therefore prone to vasospasm. Nevertheless, early studies indicate that this vessel may produce an early patency rate of more than 70%. Other conduits that have been employed as coronary artery bypass grafts include the left gastroepiploic artery, splenic artery, lateral costal artery, ulnar artery, intercostal artery, lateral femoral


circumflex artery\textsuperscript{129} and left gastric artery.\textsuperscript{130} The shortage of viable conduits also has led to the use of preserved blood vessels and synthetic vascular prostheses, however they are associated with poor long-term patency.\textsuperscript{131}

**Expanded use of arterial grafting**

As a result of the excellent ITA graft patency, surgeons around the world have experimented in increasing the number of grafted coronary arteries with one ITA or using both left and right ITA and combined arterial grafting.\textsuperscript{132}

**Sequential techniques**

Sequential techniques have been used in both ITA and saphenous vein grafts and also other arterial conduits. Some risks are involved in surgical techniques.\textsuperscript{133} The sequential technique originally was used in saphenous vein grafts\textsuperscript{134}, first


reported for the ITA in 1983 by Kabbani and McBride. In 1981, Crosby and colleagues reported a prospective analysis of the angiographic and operative anatomic and reconstructive variables that influenced vein graft patency in 50 consecutive patients. Postoperative restudy showed that 18 of the 168 grafts performed were occluded due to venous disease, inadequate run-off, or sequential design error. Simple vein grafts had a 96% patency while sequential grafts had 80%. When design error for sequential grafts was eliminated, the sequential patency rate rose to 88%. In 1986, Keiser and colleagues studied sequential anastomosis grafts with a follow up time of 13 years. They concentrated specifically on 212 “double” grafts with 100% selective angiographic follow-up - 90% at 1-year and 44% at 5 years after operation. Four hundred and twenty four control single grafts were studied similarly. The patency rates of side-to-side anastomoses were much better than those of end-to-side anastomoses, whether sequential or control single grafts. Considering specifically diagonal coronary artery - left anterior descending coronary artery sequential grafts, the combined patency of all sequential anastomoses theoretically exceeds that of a comparable number of single grafts at all times of study, but the differences are small. In 1984, Tector and colleagues reported the results of sequential ITA grafts in 29 patients. The left ITA was anastomosed side-to-side to the diagonal and end-to-end to the left anterior descending coronary artery (LAD) in 24 patients, side-to-side to the proximal LAD and end-to-side to the distal LAD for proximal and mid vessel obstruction in four patients, and in one patient the left ITA was grafted


side-to-side to the first marginal branch of the circumflex artery and end-to-side to the second marginal branch. There were no operative deaths but one patient died 10 months after surgery from viral pneumonia. There was no evidence of left ventricular failure. None of the patients suffered perioperative myocardial infarction or return of their angina. Eleven patients underwent postoperative stress tests and the results were all negative. Graft visualization in three patients showed patent grafts without kinking or narrowing. In 1986, Orszulak and colleagues compared efficacy of sequential anastomoses of the ITA to the left anterior descending and diagonal coronary arteries in 40 patients and sequential saphenous vein grafts in 58 patients. Treatment with dipyridamole (starting 48 hours before operation) and aspirin (added 7 hours after operation) was given to the 40 patients with ITA grafts and to 32 of the 58 patients in the saphenous vein group. After the bypass procedure, mean blood flows were as follows: 68 ml/min in patients with ITA grafts, 73 ml/min in patients who received saphenous vein grafts and a placebo, and 99 ml/min in those who received saphenous vein grafts, aspirin, and dipyridamole. Early patency of sequential ITA grafts to the diagonal and left anterior descending coronary arteries was comparable to that of sequential saphenous vein grafts. In 1995, van Brussel and colleagues reviewed 428 consecutive patients who underwent isolated venous coronary artery bypass graft surgery. Follow-up was 99.8% complete and averaged 15.4 years for the survivors. They found that revascularization with sequential grafts only, and obesity at operation were incremental risk factors for acute myocardial infarction using the Cox regression model. In 2000, Dion and colleagues reported the graft patency in the first consecutive 500 patients receiving at least one sequential ITA who had a late angiographic restudy at a mean interval of 7.4 (range 1-12.2)
years.\textsuperscript{143} The patency rate of the sequential ITA was 96.1%. There was no significant difference between the patency of the proximal and the distal sequential ITA anastomoses. The sequential anastomoses constructed in the length tend to remain more patent than the diamond-shaped ones: 97.2% vs. 91.5% (\(P=0.004\)). In 2001, Dion and colleagues reviewed the same group of patients and found a significant difference between the saphenous vein graft patency and intactness of sequential versus single anastomoses: 76% versus 60% and 64.5% versus 44.4% at 5 and 10 years, respectively.\textsuperscript{144} There was no significant difference in either patency or intactness between right ITA and sequential saphenous grafts anastomosed to the right coronary artery: 83.4% versus 75.2% and 77.8% versus 62.4%, respectively. The same was true for the anastomoses to the “remote area” (distal circumflex, distal right coronary artery). Therefore complementary sequential saphenous grafting still deserves consideration in some patients below 70 years of age, particularly for those with disease in the “remote area”.

**Bilateral internal thoracic artery**

The first report of the use of bilateral ITA was by Suzuki in 1973.\textsuperscript{145} In 1985, Barner and colleagues reported their 12 years’ experience of 1,000 isolated coronary bypass patients with at least one ITA, and 103 of them had bilateral ITA grafts.\textsuperscript{146} There were 1,158 ITA and 1,395 vein grafts anastomoses, for a total of 2,556 grafts (2.5 per patient). The followed up time was 1 to 12 years (mean 6.3 years). Graft patency was assessed by 1,029 follow-up catheterisations in 519 patients. The patency rate of the left ITA was 96.4% at 1 year, 88.1% at 5 years, and 88.1% at 10 years. That of the right ITA was 92.8% (\(P = \text{not significant}\)) at 1


year, 84.6% ($P = \text{not significant}$) at 5 years, and at 10 years the numbers were too small to be meaningful. Comparison of patency rates for all ITA grafts with vein grafts gave 1 year graft patency rates of 95.7% versus 93.4% ($P<0.025$), 5 year rates of 87.9% versus 74.0% ($P<0.001$) and 10 year rates of 83.0% versus 41.0% ($P<0.001$). Morbidity and mortality for patients having ITA grafting are comparable to those of patients having saphenous vein bypass only.

The concern in using the bilateral ITA is the risk of sternal ischemia and infection.\textsuperscript{147} In 1992, Carrier and colleagues evaluate the effect of median sternotomy and ITA dissection on sternal vascular supply. Sternal bone tomography was performed at 7 days and one month after cardiac operation in 67 patients.\textsuperscript{148} After median sternotomy without single or bilateral ITA grafts, the average hypoperfusion ratio was 4 ± 1% compared with 13 ± 3% after single ITA grafts and 24 ± 6% after bilateral ITA grafts ($P < 0.0001$). Diabetic patients without ITA, with single ITA, and with bilateral ITAs showed hypoperfusion areas of 5 ± 3%, 15 ± 5%, and 23 ± 9%, respectively, a result similar to that of non-diabetic patients. One month after operation the hypoperfusion area decreased to 2% ± 2% ($P < 0.05$) in restudied patients. The risk of sternal complication is higher in obese patients.\textsuperscript{149} The benefit of right ITA in elderly patients is


questionable. In 1986, Lytle and colleagues reviewed the first 500 patients (420 men, 80 women, mean age 55 years, range 24 to 78) undergoing bilateral ITA grafting.\textsuperscript{150} The major complications did not correlate with gender, diabetes, number of grafts or preoperative left ventricular function but were associated with increasing age ($P = 0.0001$) and previous cardiac surgery ($P = 0.009$). The complications were decreased by the use of cardioplegia ($P = 0.002$). In 1994, He and colleagues examined the risk of death in 512 elderly patients (70 years and older) undergoing ITA grafting.\textsuperscript{151} The operative mortality in these patients was 7.62\% (39 of 512), significantly higher than that (1.97\% [60 of 3,047]; $P < 0.0001$) in younger patients (i.e. under 70 years old). Of 53 variables examined, using univariate analysis, nine preoperative variables (age, smoking history, congestive heart failure, myocardial infarction, New York Heart Association functional class, ejection fraction, left main artery disease, stenosis of the left anterior descending artery and re-operation), three intraoperative variables (emergency operation, bilateral ITA and right ITA), and nine postoperative variables were significantly associated with the higher mortality ($P < 0.05$). The significant preoperative and intraoperative variables and variables that exhibiting a tendency for correlation ($P < 0.2$) to mortality were included in a stepwise multiple logistic regression. The regression analysis demonstrated that right ITA, re-operation, history of myocardial infarction, age, left main artery disease, history of smoking and postoperative complications are the risk factors for the elderly undergoing ITA grafting. In 1996, a prospective multicentre study comprising 1830 patients in 10 units over a 4-month period were undertaken: 960 underwent coronary artery bypass grafting and 870 other procedures.\textsuperscript{152} According to the Centers for Disease Control and Prevention definitions, 2.3\% of patients (42/1830) acquired a deep sternal wound infection. Independent risk factors for deep sternal wound infection were obesity, coronary artery bypass


grafting, reoperation, and postoperative inotropic support. Independent risk factors after coronary artery bypass grafting were obesity, bilateral ITA grafting, reoperation, and postoperative inotropic support.

In 1998, Buxton and colleagues demonstrated the benefit of the use of bilateral ITA.\textsuperscript{153} Two thousand eight hundred and twenty six patients (age 62 ± 9 years [mean ± 1 SD], 2350 men, mean follow-up 52 months) who underwent surgery with ITAs, supplemented by saphenous vein grafts were reviewed. Single ITA grafting (n = 1557) was compared with double (n = 1269) using the Cox proportional hazards model. Significant predictors of all-cause mortality were as follows: (1) peripheral vascular disease, rate ratio (RR) = 2.4 (1.7 to 3.4 [95% CI]); (2) prior myocardial infarction, RR = 2.1 (1.5 to 3.1); (3) severe left ventricular dysfunction, RR = 3.9 (2.6 to 5.9) and moderate left ventricular dysfunction, RR = 2.0 (1.5 to 2.6); (4) age ≥ 70 years, RR = 3.4 (2.4 to 4.8), and age 60 to 69 years, RR = 1.7 (1.3 to 2.4); (5) diabetes mellitus, RR = 1.7 (1.3 to 2.4); (6) carotid disease, RR = 1.7 (1.2 to 2.4); and (7) single ITA (versus bilateral ITA), RR = 1.4 (1.1 to 1.8). Single ITA was also a predictor of all-cause mortality, late myocardial infarction, or late reoperation (RR = 1.3 [1.1 to 1.6]).

In 1999, Lytle and colleagues reviewed a group of patients who had undergone elective primary isolated coronary bypass grafting and received either single (8123 patients) or bilateral ITA grafts (2001 patients), with or without additional vein grafts with a mean follow-up of 10 years.\textsuperscript{154} In-hospital mortality was 0.7% for both the bilateral and single ITA groups. Survival rates for the bilateral ITA group were 94%, 84% and 67%, and for the single ITA group 92%, 79% and 64% at 5, 10, and 15 postoperative years respectively (\(P<0.001\)). Death, reoperation, and percutaneous transluminal coronary angioplasty were more frequent for patients undergoing single rather than bilateral ITA grafting. This


observation remained true despite multiple adjustments for patient selection, sampling, and length of follow-up.

**Skeletonized internal thoracic artery**

The first report of skeletonized ITA was by Keeley in 1987. In 1992, Parish and colleagues investigated chest wall blood flow in a canine model measured with radioactive microspheres. Chest wall blood flow was significantly decreased from preharvest levels after ITA harvesting regardless of the technique used. Tissue blood flows decreased to 46.9%, 22.1% and 41.2% of baseline values for the manubrium ($P < 0.01$), sternum ($P < 0.001$) and ribs ($P < 0.05$), respectively. Residual sternal blood flow on the side of the skeletonized vessel was significantly greater than on the side of the pedicle graft ($2.60 \pm 0.68$ versus $1.27 \pm 0.27$ cm$^3$/min/100 gm, $P < 0.001$). In 1999, Calafiore and colleagues reported results of 1,146 patients who underwent isolated CABG using bilateral ITAs, 304 receiving pedicled grafts (group A, October 1991 through May 1994) and 842 skeletonized conduits (group B, June 1994 through June 1998). Group B had a higher incidence of patients with diabetes (223 versus 40, $P < 0.001$). Seventy-one patients in group A and 133 (15.8%) in group B underwent postoperative angiography. The patency rate was similar, both early (100% in group A versus 98.6% in group B, not significant) and late (98.6% in group A versus 98.4% in group B, not significant). In 1999, Gaudino and colleagues compared the morphology of ITA harvesting by skeletonized and pedicled techniques in 40 consecutive patients undergoing coronary artery bypass. They were randomized to receive a skeletonized (n = 22) or a pedicled (n = 18) ITA graft. There was no difference in endothelium integrity in both groups.

**Composite T or Y graft**

This technique has allowed surgeons to expand the use of the ITA and also benefit patients with an aorta disease. Mills introduced the concept of connecting

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one ITA to the other in 1982. In 1986, Tector and Sauvage published articles about this technique.\textsuperscript{157} In 1994, Tector reported early results in 486 patients undergoing total coronary artery revascularization using a T-graft constructed from the attached left LITA and the free right ITA with an average of 4.34 distal anastomoses.\textsuperscript{158} The mortality at 30 days was 2.3%; two of 92 women and 9 of 394 men died. The perioperative infarction rate was 1.2%. Postoperative angiography in 34 patients showed 98.3% of left ITA and 86.5% of right ITA anastomoses to be patent. In 1994, Calafiore and colleagues reported the results of complex arterial CABG performed on 130 patients between October 1991 and May 1993.\textsuperscript{159} One hundred and thirty six complex arterial conduits (branched, lengthened or both) were constructed using 360 arterial conduits, 163 as free grafts (three left ITAs, 16 right ITAs, 86 inferior epigastric arteries, 57 RAs, and one right gastroepiploic artery). One hundred and fifty four free grafts were anastomosed to one or both ITAs and one to an RA. There was no operative mortality and no inotropic or mechanical supports were used. The overall mortality rate was 1.5%. Early angiographic controls (between the 7th and 15th postoperative days) demonstrated 100% patency; late angiographic controls (at a mean interval of 9.5 months after operation) documented a mean patency rate ranging from 94.1% of the RAs to 100% of the left ITAs and right gastroepiploic arteries. At a mean follow-up of 7.2 months (range: 1 to 15 months) all patients are alive without recurrence of symptoms. In 1995, Calafiore and colleagues reported patency rates of 93.1% for the RA and 95.7% for the inferior epigastric artery at a mean follow-up of 18.5 ± 10.4 months (range: 1 to 39 months) using a composite graft in 240 patients comprising 163 RAs and 124 inferior epigastric arteries with one (224 instances) or both (two instances) ITAs as inflow.


In 2000, Calafiore and colleagues compared the results of patients having in situ ITA (n = 1378, group A) or Y grafts (n = 440, group B). The number of anastomoses per patient and the number of bilateral ITA anastomoses per patient were higher in group B (3.1 ± 0.9 and 2.7 ± 0.9) than in group A (2.9 ± 0.8 and 2.2 ± 0.6) (both P < 0.001). The number of right ITA anastomoses per patient rose from 1.0 ± 0.3 in group A to 1.4 ± 0.6 in group B (P < 0.001), and the number of sequential anastomoses per right ITA graft increased from 4.1% to 34.3% (P < 0.001). Eight-year survivals were 95.8% ± 2.7% in group A versus 94.8% ± 4.0% in group B (P = not significant). Event-free survivals were 95.2% ± 2.9% in group A versus 93.6% ± 4.4% in group B (P = not significant). Early angiograms were obtained in 295 patients (945 anastomoses, 863 distal and 82 proximal Y grafts) comprising 213 patients in group A and 82 patients in group B. The patency rate was 98.8% in group A and 96.0% in group B (P = not significant), whereas the grade A patency rate was 97.2% in group A and 96.4% in group B (P = not significant). Late angiograms were obtained in 88 patients (25 in group A and 63 in group B) at a mean of 17.5 ± 18.4 months: the patency rate was 100% in group A and 99.2 in group B (P = not significant), and the grade A patency rate (excellent graft with unimpaired runoff) was 98.6% in group A and 98.8% in group B (P = not significant). No Y anastomosis was occluded or stenosed.

In 2001, Iaco and colleagues reported the RA graft patency in 164 RAs. In group A (128), the RAs were connected end to side (115) or end to end (13) to

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the left ITA. In group B, 36 proximal anastomosis of the RAs were anastomosed on the ascending aorta. Eight-year survival was 83.2% ± 3.2% (group A 82.1% ± 3.8% and group B 86.7% ± 6.2%, \( P = \text{not significant} \)). Event free survival was 80.1% ± 3.5% (group A 79.9% ± 4.4% and group B 80.2% ± 7.3%, \( P = \text{not significant} \)). Sixty-one patients (37.2%) had early angiography within 90 days of the operation. The patency rates of RA distal anastomoses were 98.9% (88 of 89), in group A, the patency rates of RA distal anastomoses was 98.7% (77 of 78), in group B 100% (11 of 11; \( P = \text{not significant} \)). After a mean of 48 ± 27 months (6 to 96), 72 patients (51.1% of the survivors) had a repeat angiogram. The patency rate of RA distal anastomoses was 95.6% (87 of 91). In group A, the patency rate of RA distal anastomoses was 93.8% (61 of 65) and in group B 100% (26 of 26; \( P = \text{not significant} \)). All the intermediate RA-left ITA anastomoses were patent at the early and late control angiogram. The patency rates for RA and ITAs were similar both early (88 of 89 versus 82 of 82; \( P = \text{not significant} \)) and after 48 ± 27 months (87 of 91 versus 93 of 93; \( P = \text{not significant} \)).

Concerning the flow in the graft after multiple distal anastomoses from a single graft, with either sequential anastomoses or a Y-graft. In 1984, Minale and colleagues performed an aorto-coronary by-pass graft to the left anterior descending artery and to a major diagonal branch in 35 patients.\(^{164}\) Flows through the by-passes were measured electromagnetically during the operation. Flow to left anterior descending artery was significantly higher through an isolated by-pass than through a sequential by-pass. Flow to diagonal branch showed no significant difference in the two groups. However this was a study in the saphenous vein graft. In 1986, Lee and colleagues demonstrated the ability of the ITA in increasing the flow in the canine ITA.\(^{165}\) The left ITA was anastomosed to the circumflex coronary artery. In situ, blood flow in the ITA was 27 ml/min. Blood flow was 63 ml/min in the circumflex coronary artery and 42 ml/min in the


left anterior descending coronary artery. After anastomosis of the ITA to the circumflex coronary artery, the left main coronary artery was ligated; flow through the bypass graft increased to 92 ml/min, and systemic hemodynamics remained stable. Isoproterenol stimulation further increased flow through the ITA to 160 ml/min.

In 1999, Wendler performed a flow study comparing two types of grafts (right ITA or RA) in the composite T graft in 251 patients. Flow was measured in the proximal left ITA with a Doppler guide wire at one week and six months after the operation. At angiography (n = 142, 56.6%) the patency rate was 96.3% (right ITA group) versus 98.2% (RA group). There was no significant difference between baseline flow, maximum flow, and coronary flow reserve between the two groups. Coronary flow reserve increased in both groups within the first six postoperative months (right ITA group, 1.85 ± 0.31 vs. 2.77 ± 0.77, \( P = 0.0002 \); RA group, 1.82 ± 0.4 vs. 2.53 ± 0.73, \( P = 0.009 \)).

In 2000, Speziale and colleagues studied the flow in the composite Y arterial grafts in 76 patients. All patients received sequential grafting by using both ITAs, inferior epigastric and RGEA joined as a composite Y graft. All patients except one showed good flow (ml/min and waveform) in either branch of composite graft. Temporary occlusion of either branch did not significantly affect flow in the other side of the arterial Y. Mid-term follow-up (three and 15 months) and angiographic studies showed a high graft patency rate. Flow reserve of the left ITA did not affect blood flow and resistance on either branch of the Y graft when temporary occlusion on the other side of the arterial Y was performed. However the blood flow in the bypasses was affected by the degree of stenosis in native

coronary artery.\textsuperscript{167} There was a higher flow in the graft when the native coronary had more severe stenosis or occluded.

In 2000, Wendler and colleagues, using combined skeletonized ITA and T graft, performed complete arterial grafting in 490 patients with two arterial conduits, either both ITAs (23\%) or the left ITA and RA (77\%).\textsuperscript{168} Triple-vessel disease was present in 88\% of the patients. T graft was performed in 85\% of the patients. The rate of perioperative myocardial infarction was 1.2\%. Hospital mortality was 2.2\%. Postoperative coronary angiography in 172 patients (35\%) documented excellent patency rates at one week after surgery (left ITA 98.3\%, right ITA 96.5\%, and RA 96.6\%). In 2001, Wendler and colleagues demonstrated a good outcome of coronary artery bypass grafting in diabetic patients using skeletonized ITA, RA and T graft techniques.\textsuperscript{169} Bilateral ITA graft was used in 20\% of patients. Sternal complication and in hospital mortality was not different when compared with non diabetic patients who had complete arterial grafting with the same technique.

Also in 2001, Tector and colleagues reported a series of purely ITA reconstruction in 897 patients with a total of 3,784 ITA grafts (4.2 grafts per patient).\textsuperscript{170} Early mortality for the group was 2.3\%. Freedom from death was 86\% and freedom from reintervention was 94\% at five years after the operation. In the same year, Barner and colleagues reported 7-year experience with the ITA/RA T graft as the only conduits.\textsuperscript{171} There were 909 patients with a mean age of 60 and


20% age 70 or older. The incidence of triple-vessel disease was 73%, female gender 28%, diabetes mellitus 27%, peripheral vascular disease 11%, cerebrovascular disease 10% and chronic obstructive pulmonary disease 6%; ejection fraction was less than 35% in 11%. Follow-up information was obtained at a mean of 35.4 months (range 1-88) and was 95% complete. Operative mortality was 0.08%. The incidence of perioperative infarction was 3.3%, low cardiac output 2.7%, stroke 2.2%, reoperation for bleeding 3.8%, and deep sternal infection 0.8%. The actuarial survival rate was 90% at 5 years, freedom from infarction was 94%, freedom from catheterization was 83%, and freedom from reintervention (angioplasty or reoperation) 93.

All of these procedures are technical demand and run a risk of major multiple grafts failure because in some procedures the inflow comes from one source. One anastomosis problem can cause large myocardial ischemia. There is no long term data on atherosclerosis on T or Y graft, in addition naturally the atherosclerosis often is prone to occur at the origin of the side branch. One unfavorable target artery, e.g. poor run off, might cause complete graft failure. The combined use of several techniques might achieve an excellent long-term outcome with a minimal risk such as combination of bilateral ITA in which one side skeletonized and one side pedicle, with some other arterial conduits such as RA or gastroepiploic artery. Y or T graft reserve in case there is insufficient number of conduit or length of the graft.

**Vasoreactivity of vascular grafts**

One of the key successes of arterial grafting has been the elimination of vasospasm of the graft during intraoperative and postoperative periods. He GW and colleagues have extensive studies on this subject. The following points summarise the key issues.
1. Different vessels react differently to vasoconstrictors and vasodilators.\textsuperscript{172} Glyceryl trinitrate (GTN) caused relaxation of the ITA, saphenous vein and coronary artery but was less sensitive, less potent and had a reduced range of relaxation in the ITA. Shapira and colleagues demonstrated the superiority of GTN in dilating RA, ITA and saphenous vein compared with the diltiazem.\textsuperscript{173} Zabeeda and colleagues proves the efficacy of intravenous GTN as a systemic vasodilator for in vivo vasodilation of both the ITA and RA.\textsuperscript{174} Hillier found that in the human ITA, the use of intraluminal papaverine increased the lumen size by 20\% ($P < 0.05$), and the contractions elicited by noradrenaline were significantly less in the papaverine group than in the control group ($P < 0.05$).\textsuperscript{175} Endothelium-dependent relaxation to acetylcholine or bradykinin was not affected by papaverine treatment. Endothelium-independent relaxation was the same in both groups, with almost 100\% relaxation achieved by sodium nitroprusside. He and colleagues found that papaverine was less sensitive in the ITA as compared with the coronary artery and saphenous vein. Nifedipine, verapamil, and diltiazem were potent relaxing agents in all three vessels when pre-contracted by potassium chloride (K$^+$), but less potent in vessels contracted by the thromboxane mimetic U46619 or phenylephrine, especially in the saphenous vein. Pretreatment of vessels with GTN failed to alter subsequent contraction to U46619 or K$^+$ while nifedipine pretreatment abolished subsequent contraction to K$^+$ and reduced sensitivity of the ITA to U46619.\textsuperscript{176} Therefore perioperative ITA spasm could be treated with the rapid-onset, nonspecific, vasodilator glyceryl trinitrate, but for prophylaxis of ITA spasm, calcium antagonists or specific receptor antagonists

\textsuperscript{172} He, Angus and Rosenfeldt. Journal of Cardiovascular Pharmacology 1988; 12:12-22.


\textsuperscript{176} He, Rosenfeldt, Buxton and Angus. Circulation 1989; 80:1141-50.
should be tested in the clinical setting. Beta-adrenoceptors contribute little to the reactivity of the human ITA graft to sympathomimetic drugs.\textsuperscript{177} The postjunctional alpha-adrenoceptors are predominantly of the alpha 1-subtype in the human ITA and therefore the alpha-adrenoceptor agonist-induced contraction and the sympathetic nerve stimulation-induced contraction is mediated mainly by activation of the alpha 1-adrenoceptors.\textsuperscript{178} This is also true for the RA. The human RA is an alpha-adrenoceptor-dominant artery with little beta-adrenoceptor function.\textsuperscript{179} The use of beta-blockers is not likely to evoke the spasm of the RA. Furthermore, the RA has a dominant alpha1-adrenoceptor function. Circulating catecholamines will mainly contract the RA by activation of the alpha1-adrenoceptors and to a lesser extent also by alpha2-adrenoceptors. Dipp and colleagues demonstrated the efficacy of phenoxybenzamine (alpha-antagonist) in the prevention of RA spasm for at least 6 hours.\textsuperscript{180} Phenoxybenzamine’s effect is longer lasting than papaverine and is also less harmful to the endothelium compared with papaverine. The distal section of the human ITA is the most reactive part of the graft to some vasoconstrictors (norepinephrine and endothelin-1) compared with the middle and the proximal sections.\textsuperscript{181} In contrast the proximal part of the RA showed a significantly greater response to K\textsuperscript{+} than that of distal RA and both contracted more than the left ITA and the right ITA.\textsuperscript{182} There was no difference in the response to noradrenaline and adrenaline between proximal and distal RA, both of which contracted more than the left and right


ITA. Comparing the ITA with the inferior epigastric artery, both respond the same to vasoconstrictors e.g. potassium, norepinephrine, U46619 and endothelin-1. The responses to vasorelaxants e.g. glyceryl trinitrate or acetylcholine are also the same. However, a non-receptor agonist for endothelium-derived relaxing factor e.g. A23187 induced significantly less relaxation in the inferior epigastric artery than in the ITA. Mugge and colleagues demonstrated that the endothelium-independent relaxation in response to nitroglycerin was identical in both inferior epigastric artery and ITA.\textsuperscript{183} In contrast, the endothelium-dependent relaxation in response to acetylcholine, substance P, and bradykinin was significantly greater in the inferior epigastric artery than in the ITA. Comparing the ITA with the RA, the human RA has a higher receptor-mediated contractility (to endothelin-I and angiotensin-II) but similar response to either endothelium-dependent (substance P and A23187) or endothelium-independent (nitroglycerin) relaxation compared to the ITA.\textsuperscript{184} However, Cable and colleagues demonstrated diminished endothelial regulation of vascular smooth muscle in the RA compared with the ITA.\textsuperscript{185} Comparing the ITA and the RGEA, Yang and colleagues found that norepinephrine and $K^+$ evoked threefold greater contraction in the RGEA than in the ITA ($P < 0.01$ to 0.05), whereas the sensitivity to the catecholamine was comparable.\textsuperscript{186} Acetylcholine induced endothelium-dependent relaxations in the RGEA and ITA, but the sensitivity and maximal relaxation were slightly less in the RGEA than in the ITA ($P < 0.05$). Histamine induced endothelium-dependent relaxation showed a similar sensitivity, whereas the maximal relaxation was slightly enhanced in the RGEA. Comparing the ITA, RA and the RGEA, Chardigny and colleagues found that the RA had stronger contractions to $K^+$ than


the other vessels. The radial and the gastroepiploic arteries with endothelium presented a higher contraction force than the ITA in response to norepinephrine and serotonin. The three vessels had equal sensitivities to norepinephrine and serotonin. The RGEA had a lower response to thromboxane A2 mimetic than the two other vessels.

2. A combined solution of glyceryl trinitrate-verapamil provides a rapid onset and long action for use in preparing the saphenous vein, RA and ITA. Both nitroglycerin and sodium nitroprusside are potent vasodilators in the RA. Nitroglycerin may have more potent effects in certain situations (constriction related to thromboxane A2). However, tolerance to nitroglycerin may develop. A cross tolerance to sodium nitroprusside may exist but the effect is weak so that sodium nitroprusside may be preferable to nitroglycerin as a vasodilator in the RA postoperatively. Other vasodilators may be the drugs of choice under such circumstances. Although all calcium channel antagonists have antispastic effects in the RA, they have different sensitivities. Dihydropyridine derivatives may be the most potent calcium channel antagonists. Phosphodiesterase III inhibitors are potent vasodilators of human ITA and may have a slight selectivity with greater potency to receptor stimulants than to the depolarizing agent K⁺. Phosphodiesterase III inhibitor-induced relaxation is also not affected by denudation of endothelium. Phosphodiesterase III inhibitor is also a potent


vasodilator for the RA, with possibly higher potency when mediated by alpha-adrenoceptor- and depolarizing agent K⁺, but less potency in thromboxane A(2)-mediated, contraction.¹⁹² Neither dobutamine nor dopexamine caused vasoconstriction from baseline tension, whereas vessels exposed to dopamine showed constriction at high concentrations.¹⁹³ The vessel responses to the dopaminergic agents did not differ according to the functional status of the endothelium as initially assessed by acetylcholine-induced vessel relaxation.

3. "Vasoactivator" substances have been named because the previous known of vasoconstrictors also demonstrated a vasodilatation effect through the mechanism of endothelium-derived relaxing factor (EDRF) release.¹⁹⁴ This “vasoactivator” may be classified as (1) Type I: vasoconstriction-predominant type such as acetylcholine and U46619 in porcine which mainly cause contraction in endothelium-intact arteries; (2) Type II: balanced type such as norepinephrine and 5-hydroxytryptamine in porcine coronary artery which cause little contraction in endothelium-intact arteries but a great contraction when the endothelium is denuded.¹⁹⁵

4. In 1995, He and colleagues proposed the classification of arterial conduits into three types based on pharmacological reactivity of the grafts and anatomical locations: type I: (somatic arteries) e.g. ITA and inferior epigastric artery, type II: (splanchnic arteries) e.g. gastroepiploic artery, and type III: (limb arteries) e.g.


RA. Types II and III are prone to spasm because of higher contractility whereas type I arteries are usually less spastic.

The development of coronary artery surgery up until 1990 is summarized in figure 1.

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The Role of the Radial Artery as a Bypass Graft

Early Patency

In 1992, Acar and colleagues published the results of a study of 104 patients who received 122 RA grafts. They found that the patency rate of the radial arteries was 93.5% at 9 months, better than the reported patency of free internal thoracic arteries (69.3%). This improvement was thought to be due to better harvesting techniques, the use of calcium channel blocking agents, and the administration of aspirin. Following Acar’s findings, several cardiac centers in Europe and North America confirmed these results, finding excellent patency rates at early to mid-term follow-up. Brodman and colleagues in 1996 reported a patency rate of 95.7% at 12 weeks while Calafiore and associates in 1995 demonstrated a patency rate of 94% at a mean of 14 months. More recently, Acar and colleagues confirmed the long-term patency of RA grafts, reporting a patency rate of 83% at 5 years compared with 91% for the LITA grafts. The authors suggested that the difference in patency may have been due to the fact that the two conduits were grafted to different target arteries. The RA was anastomosed to small vessels, while the LITA, for the most part, was grafted to the LAD.

Conclusion

As indicated in the introduction to this chapter, the history of the surgical treatment of coronary artery disease has been far from linear but the summary of


events presented in figure 1 show a clear progression from indirect to direct methods of surgical treatment. One of the most useful developments in recent years is the direct coronary revascularization using arterial conduits for CABG. The need for a viable alternative to the ITA has seen a growing interest in the RA, a vessel that offers excellent potential as a bypass graft. Despite recent reports that the RA has high short and mid-term patency rates, more investigations are needed before it can be viewed as a vessel for CABG. The central aim of this thesis is to closely examine the potential role of the radial as a coronary artery graft. The main issues addressed in the thesis relate to the suitability, safety and effectiveness of the RA as a conduit for CABG. Accordingly, the three interconnected hypotheses presented below attempt to address these specific issues.
(b) **Hypotheses and Specific Aims**

This thesis posits three main hypotheses.

**First Hypothesis:** The radial artery (RA) is a suitable conduit for coronary artery bypass grafting in most patients.

The specific aims are:
1. To examine the anatomy and anatomical variations of the arteries of the upper extremity.
2. To document the prevalence of RA disease (intimal hyperplasia, atherosclerosis and medial calcification) in a group of patients selected for coronary artery bypass grafting (CABG).
3. To compare the pre-existing disease processes in the RA with those of the internal thoracic artery in patients undergoing CABG.

**Second Hypothesis:** The harvesting of the RA is safe.

The specific aims are:
1. To outline the collateral circulation of the hand, or more specifically, to define the anatomical connections (including the variations) between the RA and other arteries in the hand.
2. To validate the modified Allen test using digital systolic blood pressure via photophlethysmography and Doppler ultrasound as points of comparison.

**Third Hypothesis:** The RA is an effective alternative to other conduits commonly used for coronary artery bypass grafting.

The specific aims are:
1. To compare the survival rate in patients who receive the RA, right internal thoracic artery or the saphenous vein graft as a second graft for CABG.
2. To compare RA graft patency with that of the internal thoracic artery and the great saphenous vein.
Chapter 2
Surgical Anatomy and Variations of the Arterial System of the Upper Extremity

Introduction

(a) Surgical Anatomy of the Arterial System of the Upper Extremity

Development of the Arterial System of the Upper Extremity

Normal Arterial Systems of the Upper Extremity

The Arm
   The Brachial artery

The Forearm
   The Radial artery
   The Ulnar artery

Anatomical Consideration for Radial Artery Harvesting
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   Surgical Exposure

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Variations of the forearm arteries
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   Radial artery
   Deep palmar arch of the radial artery
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   Superficial palmar arch of the ulnar artery
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Discussion

Variations of the arteries in the forearm
Variations of the arterial connections in the hand
Introduction

Intermittent reports have indicated that radial artery (RA) harvesting has some potentially serious complications including radial nerve injury\(^{200}\) and impaired hand circulation\(^{201}\). Several other RA interventions such as vascular access for hemodialysis and percutaneous RA catheterization also cause hand ischemia\(^{202}\). In 1998 Morsy and colleagues reported an incidence of hand ischemia of 4.3% (13 of 299 arteriovenous grafts) and 1.8% (2 of 110 direct forearm arteriovenous fistulas)\(^{203}\). There were sporadic reports of hand ischemia after RA cannulation, but in 1983, Slogoff and colleagues reported the frequency of complications after RA cannulation in 1,699 cardiovascular surgical patients and in 83 patients in whom cannulation was performed in another artery after failure at the radial site\(^{204}\). RA flow was determined by a Doppler technique 1 day


and 7 days after decannulation. Although partial or complete RA occlusion after decannulation occurred in more than 25% of the patients, no ischemic damage to the hand or disability occurred in any patient. Generally, the causes of hand ischemia include previous trauma, vascular pathologies or anatomically insufficient arterial collateral blood supplies. The last factor may be due to dominance of the RA or absence of the ulnar artery. In addition to possessing competency in basic surgical techniques, the surgeon must have a detailed knowledge of the anatomy and variations of the blood supply of the upper limb in order to avoid these complications.

The aims of this chapter are to investigate: 1) the suitability of the RA as a bypass graft in terms of the ease with which the vessel can be accessed and harvested by assessing the surgical anatomy of the forearm arteries; and 2) the collateral circulation in the forearm and hand to ascertain whether it is safe to routinely remove the RA. Accordingly, the first part of this chapter reviews the current literature pertaining to the normal vascular anatomy of the upper extremity. Given the lack of information in standard anatomy textbooks regarding crucial variations in the circulation of the upper limb, the second part of the chapter discusses the results of a study undertaken by me and others of the upper extremities of 50 cadaveric upper extremities.

a) Surgical Anatomy of the Arterial System of the Upper Extremity

Development of the Arteries of the Upper Extremity

In order to contextualize the variations of the arterial blood supply of the upper extremity, this section first briefly reviews the embryologic development of the circulation of the upper limb. The embryologic development of the arterial supply of the arm commences as vascular plexuses in the limb bud which then

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coalesce into a central artery. The main artery in the arm is axial in position and represents a continuation of the 6th cervical segmental artery. Proximally it becomes the main subclavian-axillary-brachial trunk. Initially it extends as a single main stem; below the elbow it persists in reduced form as the interosseous artery; and at the carpus, it terminates by dividing into digital branches. In the forearm it lies between two bones resting on the interosseous membrane, in the position occupied by the adult anterior interosseous artery.

At the next stage, a parallel branch - the median artery - runs with the median nerve in the forearm. The median artery gradually becomes larger and temporarily takes over the supply to the fingers, while the anterior interosseous artery undergoes a corresponding retrogression.

Both the radial and ulnar arteries form comparatively late in development. In human embryos of about 18mm crown-heel length, the ulnar artery develops as a branch from the original brachial trunk artery, extends down the ulnar side of the forearm and anastomoses with the median artery to form a superficial palmar arch from which digital branches arise. After the development of the ulnar artery, the median artery begins to regress. In adults, the RA is the residual part of the embryologic superficial brachial artery. In embryos of 21-mm length, the superficial brachial artery emerges from the axillary region and develops parallel to the original brachial artery where it lies superficial to the median nerve. After it traverses the arm, it travels down the radial side of the forearm and near the wrist, passes to the posterior surface and divides over the carpus into branches for the dorsum of the thumb and index finger. At the next stage, the antibrachial (forearm) part of the superficial brachial artery forms the RA while the upper part of the superficial brachial artery degenerates until it is normally represented in the adult by a small branch of the brachial which passes to the biceps muscle. The deep (profunda) branch of the brachial artery and the smaller branches to the

\[206\] Senior. Anat Rec 1926; 32:220-221.
shoulder and elbow develop at a relatively late stage as new offshoots of the primary axial vessel (Figure 2.1).

**Figure 2.1** Diagrams illustrating the development of the arteries of the upper extremity. The original system (a, b). Regressed arteries (in c-f) are shown as faded.
Normal Arterial Systems of Upper Extremity

In this section I review the normal anatomy of the arteries in the upper extremities, discussing in particular: 1) the relationship between the arteries and adjacent structures; and 2) the collateral circulation of the arterial system in the arm, forearm and hand.\textsuperscript{207}

The Arm

Arteries of the upper extremity arise from the subclavian system. The subclavian artery becomes the axillary artery when it passes the lateral border of the first rib at the midpoint of the clavicle. The axillary artery enters the apex of the axilla by passing the first digitation of serratus anterior and runs from deep to superficial. It is divided into three parts by the pectoralis minor- the part above, the part behind and the part below - and changes its name to the brachial artery at the lower border of the teres major muscle.

The Brachial artery

Beginning at the lower border of the tendon of the teres major, the brachial artery runs down the arm, lying immediately under the deep fascia through which it can be palpated throughout its length. It terminates by dividing into the radial and ulnar arteries at a point about a finger’s breadth below the bend of the elbow, that is, opposite the inner border of the neck of the radius. An important surface landmark for the brachial artery runs along a line from the medial bicipital groove behind the coraco-brachialis muscle to the middle of the cubital fossa at a point level with the neck of the radius. Therefore, the surgeon can approach the brachial artery by making an incision at the medial border of the biceps, in the groove between the biceps and triceps muscles. The brachial artery lies within the neurovascular bundle under the deep fascia. The median nerve is closely related to the brachial artery. It lies lateral to the brachial artery in the upper part of the arm.

and then obliquely crosses the artery and lies medial to it in the lower part of the arm. In the upper part, the ulnar nerve lies posterior to the brachial artery, however, in the lower part of the arm, it pierces the medial intermuscular septum and lies in the groove behind the medial epicondyle of the humerus where it is readily palpable.

**Branches in the arm**

The brachial artery gives off five branches in the arm: 1) the *profunda brachii*, 2) the *superior ulnar collateral artery*, 3) the *inferior ulnar collateral artery*, 4) the nutrient artery to the humerus, and 5) the *muscular arteries*. The first branch forms anastomoses with the branches from the axillary artery and recurrent branch of the RA. The second and third branches form anastomoses with the anterior and posterior ulnar recurrent branches of the ulnar artery.

The major branch of the brachial artery is the *profunda brachii* artery. It arises from the medial and posterior aspect of the brachial artery just below the lower border of the teres major muscle. Running alongside the radial nerve, the profunda brachii artery travels backwards between the long and medial heads of the triceps and then runs along the groove with the radial nerve where it is covered by the lateral head of the triceps. It ends by forming anterior and posterior anastomotic branches with the recurrent branches of the RA. The profunda brachii artery supplies the triceps muscle and also forms anastomoses with the posterior circumflex artery.

The *superior ulnar collateral artery* is a small branch of the brachial artery arising just below the middle of the arm and running with the ulnar nerve. The inferior ulnar collateral artery arises about 5 cm above the elbow, passing medially between the median nerve and the brachialis muscle before running distally. Both superior and inferior ulnar collateral arteries form anastomoses with the ulnar collateral branch of the ulnar artery.

The nutrient artery of the humerus usually arises approximately in the middle of the arm before entering the nutrient canal and running distally.
Finally, the muscular branches of the brachial artery supply the coracobrachialis, biceps and brachialis muscles.

**The Forearm**

**The Radial Artery**

The RA arises from the bifurcation of the brachial artery in the cubital fossa and terminates by forming a deep palmar arch in the hand. The surface marking of the RA is along a line, slightly convex laterally, from a point medial to the biceps tendon in the cubital fossa to the medial side of the styloid process of the radius where pulsation can be detected between the flexor carpi radialis medially and the salient anterior border of the radius. It then runs along the floor of the anatomical snuffbox across the scaphoid bone and the trapezium, where its pulsation is obvious. Finally, it travels towards the dorsal aspect of the hand running deep into the palmar side of the hand.

The RA is accompanied by paired venae comitantes. In the upper part of the forearm it is overlapped anteriorly by the brachioradialis muscle. The distal one third is covered only by skin and by superficial and deep layers of fasciae. As it runs its course, the RA passes over the tendon of biceps, the supinator muscle, the insertion of pronator teres, the radial origin of flexor digitorum superficialis, the flexor pollicis longus muscle, the pronator quadratus muscles, and the lower end of the radius. In the middle third of its course it runs medial to the superficial branch of the radial nerve.

At its distal end it disappears beneath the tendons of the abductor pollicis longus and extensor pollicis brevis muscles to cross the anatomical snuffbox. As it passes between the heads of the first dorsal interosseous muscle it is crossed by the beginning of the cephalic vein and the digital branches of the radial nerve. In 84% of cases the normal arterial anatomy of the forearm presents as follows (Figure 2.2).
**Branches at the elbow**

Immediately below the elbow, the RA gives off the radial recurrent artery, a branch that is duplicated in some cases. It then passes between the superficial and deep branches of the radial nerve and ascends behind the brachioradialis muscle in front of the supinator and brachialis muscles; it supplies all of these muscles as well as the elbow joint. Finally, its branches run upwards, both anterior and posterior to the elbow joint, to anastomose with the descending articular branches of the profunda brachii and with the ulnar collateral arteries.

**Branches in the forearm**

The RA gives off several muscular branches supplying the muscles on the radial side of the forearm.

**Branches in the hand**

The RA gives off two carpal branches (palmar carpal and dorsal carpal branches), two palmar branches (superficial palmar branch, deep palmar branch) and three single branches (the first dorsal metacarpal artery, the arteria princeps pollicis and the arteria radialis indicis).

At the wrist the RA gives off a small palmar (anterior) and a small dorsal (posterior) carpal branch. The palmar carpal branch arises near the lower border of pronator quadratus, and, running medially across the palmar surface of the carpus, anastomoses behind the flexor tendons with the palmar carpal branch of the ulnar artery, thereby forming the palmar carpal arch. The dorsal carpal branch arises deep to the extensor tendons of the thumb. Running medially across the dorsal carpal surface under these tendons, it anastomoses with the dorsal carpal branch of the ulnar artery and with the anterior and posterior interosseous arteries to form a dorsal carpal arch. The palmar and dorsal carpal arches both lie close to the bone and supply the lower epiphyseal parts of the radius and ulna. The palmar carpal arch also sends branches distally into the hand to anastomose with the deep palmar arch, while the dorsal carpal arch, lying transversely across the distal row of carpal bones, sends three small dorsal metacarpal arteries distally into the second, third and fourth metacarpal spaces. These bifurcate into dorsal digital branches for the adjacent sides of the index, middle, ring and little fingers. Near
their origin, the dorsal metacarpal arteries anastomose with the deep palmar arch by the proximal perforating arteries, and, near their points of bifurcation, with the palmar digital branches of the superficial palmar arch by the distal perforating arteries.

The superficial palmar branch originates from the RA at the wrist before it travels to the dorsal side of the hand. It passes through, and occasionally over, the muscles of thenar eminence, which it supplies, sometimes anastomosing with the ulnar artery to form the superficial palmar arch.

The last three branches of the RA are varied and often have been neglected or not clearly described in textbooks. One branch at the dorsal side is called the first dorsal metacarpal artery. It arises just before the RA passes between the two heads of the first dorsal interosseous, and divides almost immediately into two branches that supply the adjacent sides of the thumb and index finger. The dorsal metacarpal artery provides the main blood supply to the thumb in about 15% of hands. The other two branches of the RA are on the palmar side. The first branch represents the principal artery of the thumb (in 80% of hands) and is named the princeps pollicis artery. It generally provides the largest blood supply to the deep palmar arteries which originate from the deep palmar arch, closely corresponding to the palmar metacarpal arteries of the other digits. It runs along the first metacarpal bone either anterior to the adductor pollicis or between the first dorsal interosseous and adductor pollicis muscles. At the level of the metacarpophalangeal joint and deep to the flexor pollicis tendon, the artery usually terminates as two palmar digital arteries supplying the thumb and sometimes the index finger. The last branch of the RA is the radialis indicis artery. It originates from the proximal part of the princeps pollicis artery in about 50% of cases, travels distally between the first dorsal interosseous muscle and the transverse head of the adductor pollicis muscle, and then runs along the lateral side of the index finger. It anastomoses with the digital artery supplying the medial side of the finger. At the distal border of the transverse head of the adductor pollicis, the radialis indicis artery anastomoses with the princeps pollicis artery and gives a communicating branch to the superficial palmar arch.
The ulnar artery

The ulnar artery is generally the larger of the two terminal branches of the brachial artery, extending along the inner side of the forearm into the palm of the hand where it forms the superficial palmar arch. The surface marking of the ulnar artery is along a line, slightly convex medially, from a point medial to the biceps tendon in the cubital fossa to the radial side of the pisiform bone. The lower two-thirds of its course is straight and is indicated by a line drawn from the front of the medial epicondyle to the radial surface of the pisiform bone with the forearm in full supination. At this point it runs alongside and lateral to the ulnar nerve. Immediately beyond the pisiform bone it gives off carpal branches and continues across the palm as the superficial palmar arch. Given its course, the best surgical approach to the artery is to make an incision lateral to the flexor carpi ulnaris tendon at the lower forearm and to then follow the artery upwards by displacing the flexor carpi ulnaris muscle.

In the upper part of the forearm, the ulnar artery passes obliquely to the medial side and deep to most of the flexor muscles, including the pronator teres, flexor carpi radialis, palmaris longus and flexor digitorum superficialis muscles. In its middle third, it is overlapped anteriorly by the flexor carpi ulnaris and lies upon the brachialis and flexor digitorum profundus muscles. The distal half of the ulnar artery lies upon the flexor digitorum profundus and runs between the flexor carpi ulnaris and flexor digitorum superficialis muscles. In this area, it is covered only by skin, and by superficial and deep layers of fascia.

At the wrist, it enters the palm in front of the flexor retinaculum in company with the ulnar nerve and is covered by skin, fasciae and the palmaris brevis muscle.

Branches at the elbow

Immediately below the elbow joint, the ulnar artery gives off the anterior and posterior ulnar recurrent arteries, branches that are the equivalent of the recurrent branch of the RA. The anterior branch is the smaller of the two and travels upwards between the brachialis and pronator teres muscles, supplying
these muscles and anastomosing with the superior and inferior ulnar collateral branches from the brachial artery. The posterior ulnar recurrent artery arises lower than the anterior branch, although sometimes the two arteries arise by a short common trunk. The posterior branch passes backwards and medially between the flexor digitorum profundus and flexor digitorum superficialis muscles and then ascends behind the medial epicondyle of the humerus. In the region between this point and the olecranon, it lies deep to the flexor carpi ulnaris, ascending between the two heads of this muscle and running alongside the ulnar nerve, supplies the neighboring muscles, bone and elbow joint, and anastomoses with the two ulnar collateral arteries from the brachial artery as well as the interosseous recurrent arteries.

**Branches in the forearm**

The ulnar artery gives off several muscular branches supplying the muscles on the medial side of the forearm and hand as well as the common flexor synovial sheath and the ulnar nerve. One important branch in the forearm is the *common interosseous artery*, which is about a centimetre long and arises from the ulnar artery about 2.5 centimetres from its commencement before passing backwards to the upper border of the interosseous membrane. Here it divides into two branches, the anterior and posterior interosseous arteries.

The *anterior interosseous artery* runs distally and lies anterior to the interosseous membrane. It is accompanied by the interosseous branch of the median nerve and overlapped by the adjacent margins of the flexor digitorum profundus and flexor pollicis longus. It continues its course directly downwards as far as the upper border of the pronator quadratus muscle before piercing the interosseous membrane and anastomosing with the posterior interosseous artery. It then descends to the back of the wrist in the compartment of the extensor retinaculum to join with the dorsal carpal arch. At this point it gives off four branches:

1. The *median artery*, which accompanies and supplies the median nerve, arises at the beginning of the anterior interosseous artery. However, it also often arises from the common interosseous artery. This artery is
sometimes greatly enlarged and runs with the median nerve into the palm of the hand where it may join the superficial palmar arch or end as one or two of the palmar digital arteries.

2. *Muscular branches* to the flexor profundus, flexor longus pollicis, pronator quadratus muscles and to other muscles that perforate the interosseous membrane to supply the extensors of the thumb.

3. The *medullary arteries (nutrient arteries)* of the radius and ulna which enter the foramina and distribute interiorly.

4. An *anterior communicating* branch arises from the anterior interosseous artery before it pierces the interosseous membrane, descending beneath the pronator quadratus muscle to anastomose with the anterior carpal arteries.

The *posterior interosseous artery*, usually much smaller than the anterior, passes backwards over the upper border of the interosseous membrane to enter the posterior compartment of the forearm. It appears on the back of the forearm between the supinator and abductor pollicis longus muscles, where it gives off the *interosseous recurrent artery*. The interosseous recurrent artery ascends to the interval between the lateral epicondyle and olecranon on or through the fibres of the supinator but deep to anconeus muscle and anastomoses with the middle collateral branch of the profunda brachii and with the posterior ulnar recurrent and radial recurrent arteries. The main posterior interosseous artery descends between the superficial and deep layers of extensor muscles. It ends as a very small artery, anastomosing with the anterior interosseous artery and with the dorsal carpal arch.

**Branches in the hand**

The ulnar artery divides into two carpal branches (palmar carpal and dorsal carpal branches), two palmar branches (superficial palmar branch, deep palmar branch) and forms anastomoses with equivalent branches of the RA.

At the wrist, there is a small palmar (anterior) and a small dorsal (posterior)
carpal branch. The *palmar carpal branch* is a very small artery. It runs laterally across the palmar surface of the carpus while passing behind the flexor digitorum profundus, anastomosing with the palmar carpal branch of the RA to form the palmar carpal arch. The *dorsal carpal branch*, varies in size, arises immediately above the pisiform bone and winds back under the tendon of the flexor carpi ulnaris to reach the dorsal surface of the carpus. It then passes laterally under the extensor tendons and anastomoses with the dorsal carpal branch of the RA, forming the dorsal carpal arch which provides three dorsal metacarpal arteries. Near its origin, it gives off a small branch which runs along the ulnar side of the fifth metacarpal bone and supplies the ulnar side of the dorsal surface of the little finger.

**Anatomical Considerations for Radial Artery Harvesting**

**Surgical incision**

Having outlined the normal arterial anatomy of the upper limb, in this section I briefly discuss the surgical procedure used to harvest the RA, focusing in particular on the possible anatomical risks associated with this procedure. When harvesting the RA, the skin incision is made on the ventral surface of the forearm above the RA along an imaginary line from the centre of the bent elbow to the fore part of the styloid process of the radius (Fig 2.3). The first obstacles encountered are the anterior branches of the medial and lateral antebrachial cutaneous nerves of the forearm. The *medial antebrachial cutaneous nerve*, a branch of the medial cord (C8, T1) of the brachial plexus, supplies skin on the medial side of the forearm. The *lateral antebrachial cutaneous nerve* represents the cutaneous branch of the musculocutaneous nerve, which is a branch of the lateral cord (C5-C7). This cutaneous branch supplies the skin over the lateral half of the anterior surface of the forearm and distributes branches which turn around the radial border of the forearm to communicate with the posterior cutaneous nerve of the forearm and the terminal branch of the radial nerve. If one uses the skin incision described above, these nerves should be left intact. The median vein (intermediate antebrachial vein) of the forearm is usually situated at, or near the site of the incision, and can be ligated. However, venous anastomoses near the
elbow should be preserved to prevent forearm and hand edema. Care should also be taken at the distal third of the forearm because the RA is very superficial where it lies medial to the flexor carpi radialis tendon; it is only covered by skin and subcutaneous tissue.

**Surgical exposure**

The second area of potential risk is in the middle third of the RA where the *superficial branch of the radial nerve* runs along the lateral side of the artery (Fig. 2.4). The superficial radial is a pure sensory branch of the radial nerve. It originates from the main radial nerve, soon after the nerve enters the forearm, and descends from the front of the lateral epicondyle along the lateral side of the forearm upon the supinator while running lateral to the RA and behind the brachioradialis. In the middle third of its course it runs close to the lateral side of the RA where it can be injured during RA harvesting. It leaves the artery about 7cm above the wrist passing deep to the tendon of the brachioradialis and winding round the lateral side of the radius before crossing the roof of the anatomical snuffbox. It then descends, pierces the deep fascia, and divides into five, or sometimes four, dorsal digital nerves. It supplies a number of joints in the hand, as well as the skin on the lateral two-thirds of the dorsum of hand, the dorsum of the thumb and the proximal parts of the lateral one and a half digits. However even if the superficial branch of the radial nerve is severely damaged during arterial harvesting, the region of sensory loss is confined to a coin-shaped area distal to the base of the first and second metacarpals. The considerable overlap of neural supply from cutaneous branches of the median and ulnar nerves explains why the area of anesthesia is less than expected.

The third structure at risk during this operation is the *deep branch of the radial nerve* which is the larger of the two terminal branches of the radial nerve and is a pure motor nerve. It gives off branches supplying the extensor carpi radialis brevis and supinator muscles before piercing the supinator, winding around the lateral aspect of the neck of the radius and entering the posterior compartment of the forearm. At this stage the deep branch of the radial nerve continues distally and changes its name to the *posterior interosseous nerve*. Soon
after emerging from the supinator the posterior interosseous nerve gives off: (1) three short branches supplying the extensor digitorum, the extensor digiti minimi and the extensor carpi ulnaris muscles; and (2) two long branches – a medial branch which supplies the extensor pollicis longus and extensor indicis muscles, and a lateral branch which supplies the abductor pollicis longus muscle and ends in the extensor pollicis brevis muscle. The posterior interosseous nerve terminates at the dorsum of the carpus, supplying the ligament and joints of the carpus. The deep branch of the radial nerve can be injured by deep extensive retraction at the elbow especially proximally. Severance of the deep branch of the radial nerve results in an inability to extend the thumb and the metacarpophalangeal joints of the other digits. Injury to the radial nerve at a higher level can cause wrist drop.

Thus, the four structures potentially at risk during RA harvesting are the medial and lateral antibrachial cutaneous nerves, the superficial branch of the radial nerve and the deep branch of the radial nerve. The latter structure, in particular, is cause for concern given its role in the motor function of the hand and wrist.
Figure 2.3  Radial artery harvesting. The incision was made on the ventral surface of the forearm avoiding injury to the medial and lateral cutaneous nerves of forearm. Brachioradialis muscle which covered the proximal two thirds of the radial artery was elevated by sharp dissection.

Figure 2.4  Full exposure of the radial artery. The superficial branch of the radial nerve (pure sensory nerve) lies along the lateral side of the artery.
b) Variations of the Arterial Systems of the Upper Extremities

INTRODUCTION

The major problems leading to hand ischemia following RA harvesting are: (1) dominant RA; (2) absent ulnar artery; and (3) inadequate collateral circulation. There are several studies describing the variations of the complex anatomy of the hand and forearm. However, standard anatomy textbooks lack information about crucial variations (such as the combination of an incomplete superficial palmar arch and incomplete deep palmar arch together in the same hand). Such information is very important when considering RA harvesting. For example, when the superficial palmar arch is incomplete, the RA can sometimes still be harvested safely if a complete deep palmar arch is present.

Thus, Part B of this chapter analyses arterial variations in the upper limb. In the first section I discuss a study — performed by myself and colleagues at the Department of Anatomy and Cell Biology at the University of Melbourne — examining anatomical variations in the arterial supply of the forearm and hand. This study focused in particular on the arterial connections between the superficial and deep palmar arches in the hand, the latter representing an important feature of collateral circulation of the hand. In the second section I review the literature on the arterial anatomy of the upper limb, comparing conventional anatomical accounts and the findings of our study.

MATERIALS AND METHODS

The study was carried out on 50 randomly selected cadaver upper extremities in the dissecting room at the Department of Anatomy and Cell Biology at the University of Melbourne. All of the cadavers had been embalmed soon after death. The dissection commenced with the subclavian artery and progressed to the metacarpal branches of the superficial and deep palmar arch in the hand. In the hand, the dissection focused on the arteries providing the major blood supply and the communications between the radial and ulnar arteries. Sketches and photographs were used to document the dissected specimens.
RESULTS

Variations in the arterial supply were organized into two categories, namely the forearm variations and the hand variations.

Variations of forearm arteries

The incidence of forearm artery variations was 30% (15/50). There was a high division of the brachial artery in seven extremities (14%). Three limbs possessed superficial ulnar arteries (6%). One limb possessed a superficial RA (2%).

One superficial dorsal branch of the RA was found. In this variation the RA divided into two branches about 7 cm proximal to the wrist (Fig 2.5). One ran in the normal position of the RA lateral to the tendon of the flexor carpi radialis. The other branch, the superficial dorsal branch of the RA, ran towards the dorsal aspect of the forearm and terminated by following the normal dorsal course of the RA but superficial to the extensor tendons. This artery then gave off branches to supply the thumb and form the deep palmar arch with the ulnar artery. In this case, the RA gave off a small superficial palmar branch that did not communicate with the ulnar artery. The superficial palmar branch of the ulnar artery supplied the thumb and anastomoses with the RA on the dorsum of the hand.

Three median arteries were found (6%). One originated from the ulnar artery (UA) while the other branched off the interosseous artery, ran alongside the median nerve and terminated in the middle of the palm.
Variations of the arterial connections in the hand

Radial Artery

The terminal branches of the RA at the wrist were: (1) the superficial palmar branch of the RA; and (2) the dorsal RA. The superficial palmar branch of the RA connected with the superficial palmar branch of the UA to form the superficial palmar arch in 10% (5/50) of hands (Fig 2.6, a). In the remaining 90% of cases the superficial palmar branch of the RA was absent or small (Fig 2.6, b-e) and only supplied a minor part of the thenar muscles. The main RA passed to the dorsal side of the hand under the abductor pollicis longus and extensor pollicis brevis tendons. It then pierced the first interosseous space and formed the deep palmar arch with the deep palmar branch of the UA in 94% (47/50) of hands (Fig 2.6, a, b, c and e). In three hands there were anatomical variations of the origin of the deep palmar arch. In these cases the RA formed the deep arch by passing through the second interosseous space (Fig 2.7, a and b).
Figure 2.6 Variations of the hand collateral circulation, palmar aspect of left hand. The black line represents the superficial palmar arch; the grey line the deep palmar arch; and the dotted line the dorsal artery.

a. Complete (classic) superficial palmar arch: the superficial palmar arch from the ulnar artery supplies the index finger and thumb and anastomoses with the superficial palmar branch of the radial artery in 10% of hands

b. Complete superficial palmar arch: the superficial palmar arch from the ulnar artery supplies the thumb. Complete deep palmar arch: the distal end of the deep palmar arch anastomoses with the deep palmar branch of the ulnar artery.

c. Incomplete superficial palmar arch: the superficial palmar arch does not provide a metacarpal branch to supply the thumb.

d. Incomplete deep palmar arch: no continuity is found between the deep palmar branch of the ulnar artery and the radial artery.

e. Median artery.
Figure 2.7  The origin of the deep palmar arch in which the radial artery passes to the palmar side via the second interosseous space.
(a) Dorsolateral aspect of the left wrist showing the origin of the deep palmar arch.
(b) Palmar aspect of the left wrist and hand.
SPA= superficial palmar arch; DPA= deep palmar arch
Deep palmar arch

The deep palmar arch lies on the proximal ends of the metacarpal bone and the interossei. In our samples, two types of deep palmar arches were found: 1) a complete deep palmar arch, and 2) an incomplete deep palmar arch.

*Complete deep palmar arch.* In this variation the terminal portion of the deep palmar branch of the RA had a connection with the deep palmar branch of the UA. This type of arch was found in 90% (45/50) of hands (Fig 2.6, a, b, c and e).

*Incomplete deep palmar arch.* In this variation the deep palmar branch of the RA did not have any connection with the UA at the deep palmar level. This was found in 10% (5/50) of hands (Fig 2.6, d).

Ulnar artery

The UA terminated by dividing into superficial palmar and deep palmar branches in all of the hands. The UA made no visible contribution to the dorsal side of the hand at the level of the wrist.

Superficial palmar arch

The superficial palmar arch lies just beneath the aponeurosis palmaris and rests upon the tendons of the flexor digitorum sublimis, its convex side facing distally. It is formed primarily from the terminal portion of the ulnar artery. The arch gives off four common palmar digital arteries which arise from its convex aspect and proceed distally on the second, third and fourth lumbrical muscles and the medial side of the little finger. Each of the palmar digital arteries is joined by the corresponding palmar metacarpal artery from the deep palmar arch. The latter, which is formed chiefly by the RA, then divides into a pair of proper palmar digital arteries which run along the contiguous sides of the index, middle, ring and little fingers. The palmar digital arteries supply nutrient branches to the phalanges and to the metacarpophalangeal and interphalangeal joints.
Two types of superficial palmar arch were found:

Complete superficial palmar arch. The superficial palmar arch was defined as complete when it supplied all the fingers and the ulnar side of the thumb. This variation was found in 66% (33/50) of hands (Fig 2.6, a, b, d and e), (Fig 2.8).

Incomplete superficial palmar arch. This arch was defined as incomplete when it only supplied the little, ring and middle fingers. This variation occurred in 34% (17/50) of hands (Fig 2.6 c and Fig 2.9).

Figure 2.8 Complete superficial palmar arch.

a. The superficial palmar arch. All fingers including the index finger and ulnar side of the thumb are supplied by the superficial palmar branch of the ulnar artery.

b. Superficial palmar branch of the ulnar artery supplies the thumb without anastomosed with the radial artery

c. Superficial palmar branch of the ulnar artery supplies the thumb and anastomoses with the digital branch of the radial artery from the dorsal aspect.

(T = thumb, SPA = superficial palmar arch, DPA = deep palmar arch)
Figure 2.9 Incomplete superficial palmar arch.

Only the little, ring and middle fingers, sometime ulnar side of the index fingers are supplied by the superficial palmar branch of the ulnar artery.

**Superficial palmar branch of ulnar artery**

The distal end of the superficial palmar arch of the UA communicated with the RA in only 34% (17/50) of hands. There were four types of this communication between the superficial palmar branch of the UA and the RA at the level of the arches (Fig 2.10):

a. via the superficial palmar branch of the RA (the ‘classic’ superficial palmar arch) in 10% (Fig 2.10 a),
b. via the digital branch of the dorsal RA in 18% (Fig 2.10 b),
c. via the deep palmar arch of the RA in 4% (Fig 2.10 c),
d. via the median artery and digital branch of the dorsal RA in 2% (Fig 2.10 d).

Figure 2.10 Four types of communication between the superficial palmar arch of the ulnar artery and the radial artery in the hand. a. via superficial palmar branch of RA (10%) b. via digital branch of the dorsal RA (18%) c. via deep palmar arch (4%) d. via median artery and digital branch of the dorsal RA (2%) 

SPA= superficial palmar arch; DPA= deep palmar arch
**Median artery**

A median artery was found in three cadavers (6%). One terminated at the wrist and one anastomosed with the superficial palmar arch (Fig 2.6 e and Fig 2.11). The third median artery terminated by dividing into branches to the index finger and thumb at the palmar side without anastomosing with the RA or UA.

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**Figure 2.11  Median artery**

a. The median artery at wrist runs along with the median nerve and terminates at the wrist.

b. The median artery passes the wrist and anastomoses with the ulna and radial arteries forming a superficial palmar arch.
Combined contributions of the ulnar and radial arteries

Even though the superficial palmar branch of the UA did not supply the thumb in about 34% of hands, a deep palmar branch of the UA anastomosed with the deep palmar branch of the RA in all cases. Similarly even though an incomplete deep palmar arch was found in 10% of hands, all of these cases had a complete superficial palmar arch.

DISCUSSION

Variations of the arteries in the forearm

Variations and anomalies of the arterial supply to the upper extremities in humans are common and, as previously mentioned, have significant surgical implications. A number of studies have attempted to document both the incidence and types of arterial variations. In one of the larger studies, McCormack and colleagues (1953)\textsuperscript{208} reported a series of 750 consecutive upper extremities from 386 adult cadavers (in 22 cadavers only one limb was available for study). The incidence of major variations in the brachial or antebrachial arterial patterns was 18.5% (139/750). However, considering cadavers with both extremities, the probability of finding a major variation was 30.8% (112/364). Arterial variations occurred bilaterally in 6.2% (23/364) and unilaterally in 24.5%. The prevalence of right-sided variations was slightly higher than on the left. In other studies the reported incidence of arterial variations ranges from 9% to 20%. In our series, variations of the forearm artery were found in 30% of the limbs, possibly because of the very detailed analysis of the forearm and presence of bilateral variations in cadavers. Variations of the RA were the most common.

Variations of the RA can be classified into three types: (1) an RA with a high origin; (2) the presence of a superficial RA; and (3) the absence of the RA. In McCormack and colleagues’ study, an RA with a high origin — here defined as an RA originating proximal to the intercondylar line — was found in 14.3% 

\textsuperscript{208} McCormack, Cauldwell and Anson. Surg Gynaecol Obstet 1953; 96:43-54.
(107/750) of all specimens, that is, 77% (107/139) of all arterial variations. In most cases, this artery represented the continuation of a persistent superficial brachial artery with the true brachial artery branching into the other forearm arteries in the cubital fossa. In McCormack’s series 15% (16/107) of the arteries with high origins commenced at the axillary artery while the rest (85%) arose from some part of the brachial artery. In our series, we found a high origin of the RA in 14% of all specimens, that is, this ‘anomaly’ accounted for 54.5% of all arterial variations. A superficial RA was found in only one of the limbs in our series. The third variation of the RA, namely its absence from the forearm,\textsuperscript{209} is rare and was not found in any of the limbs in our series. When this anomaly does occur, the anterior interosseous artery provides the main blood supply to the hand. The median artery is very small and the ulnar is replaced by a superficial ulnar artery. The superficial brachial and superficial radial arteries, as well as the deep palmar arch, are absent. Clinical examination may reveal absence of a radial pulse at the normal site although a pulse may be present at the anatomical snuffbox. The absence of the RA is sometimes accompanied by another limb defect such as the absence of the radius.

Others variations also found in anatomical studies include high origin of the ulnar artery, superficial brachial artery and the presence of an accessory brachial artery. The overall incidence of these variations was 12.2%, 5.75% and 0.7% respectively.\textsuperscript{210} A literature review also revealed that the superficial ulnar artery is found in 2-3% of cases.\textsuperscript{211} In our study, it was found in 6% of the limbs examined.


\textsuperscript{210} McCormack, Cauldwell and Anson. Surg Gynaecol Obstet 1953; 96:43-54.

The persistent median artery is an embryonic remnant of the axial artery of the upper limb. In general it derives from the ulnar artery (usually via the anterior interosseous artery) and occurs in 8% of cases.\textsuperscript{212} It is extremely rare for the median artery to originate from the RA.\textsuperscript{213} The median artery accompanies the median nerve which is located between the radial and the ulnar arteries. It may terminate at the wrist or contribute to the superficial palmar arch. The contribution of the median artery to the superficial palmar arch has been stated as ranging from 1.1\% to 16.1\%.\textsuperscript{214} The prevalence of a median artery was 6\% in our series.

**Variations of the arterial connections in the hand**

The blood supply of the hand is mainly provided by the radial and ulnar arteries. Additional blood supply may come from the median artery — which was present in 3 of the 50 hands (6\%) dissected in our study — and/or the interosseous arterial system. Normally however, the radial and ulnar arteries form four circuits in the hand. These circuits are made up of the anterior and posterior carpal arch at the level of the carpal bone and the superficial and deep palmar arch at the level of the mid-palmar area, that is, three circuits in the palmar side and one circuit on the dorsal side. The superficial and deep palmar arches are the most important of the circuits because they provide the blood supply to all of the fingers. Figure 2.12 shows the possible anastomoses in the hand which may provide a collateral circulation as typically demonstrated in anatomy textbooks. However, I found a number of variations which were not included.

\textsuperscript{212} Lippert. Arterial variations in man: classification and frequency c1985.


I found that the collateral blood supply of the hand is complex and often marked by variations. A number of variations of the superficial palmar arch of the UA were detected, the most common type found in this study being the complete superficial palmar arch (66%) and the complete deep palmar arch (90%). As noted, even though the superficial palmar branch of the UA did not supply the thumb in about 34% of hands, a complete deep palmar arch was present in all of these hands, thereby enabling the RA to be safely harvested.
Our study confirmed the findings from a larger series reported by Coleman and Anson in 1961.\textsuperscript{215} Of 650 hands examined, they observed a complete superficial palmar arch in 78.5% of hands. In this series, a complete superficial palmar arch was recorded when the superficial palmar branches of the RA and UA anastomosed, or when the UA reached the thumb and index finger. The classic type of superficial palmar arch (as typically demonstrated in anatomy textbooks)\textsuperscript{216} in which the superficial branch of the RA joins the superficial palmar arch of the UA, was found in 34.5% of hands. In our series, this classic type of arch occurred more rarely, being found in only 10% of hands.

In contrast, in 1988, Ikeda and associates\textsuperscript{217} reported a high prevalence of complete superficial palmar arches using the same definition (96.4% of 220 cadaver hands). They also found a higher proportion of classic superficial palmar arches (55.9%). However, in this classic type, the contribution of the RA was small in 34.6% of hands and equal in size in only 21.3% of hands.

Two large studies (Coleman and Anson 1961, 650 specimens and Ikeda et al. 1988, 220 specimens) classified the superficial palmar arch as following:

**Group I. Complete superficial palmar arch.** As defined in our study, when complete, the superficial palmar arch supplies palmar digital arteries to all the fingers including the index finger and thumb. The arches found in these studies can be subdivided into five types:

Type 1. Ulno-superficial radial arch. The superficial arch is formed by the superficial branch of the radial and the ulnar artery. This type was found in 34.5% (Coleman and Anson) and 55.9% (Ikeda et al.) of all specimens.


Type 2. Ulnar arch. This arch is formed solely by the ulnar artery. It was present in 37% (Coleman and Anson) and 25.5% (Ikeda et al) of cases.

Type 3. Ulno-median arch. The arch consists of the ulnar artery and remaining median artery. It was seen in 3.8% (Coleman and Anson) and 0.9% (Ikeda et al) of all specimens.

Type 4. Ulno-deep radial arch. In this type, the arch is formed by the ulnar artery and a branch from the radial end of the deep palmar arch. It was observed in 2.0% (Coleman and Anson) and 14.1% (Ikeda et al) of all cases.

Type 5. Ulno-medio-radial arch. The arch is composed of all three vessels. This type was found in only 1.2% (Coleman and Anson) of all specimens.

These studies demonstrate that RA harvesting should have little effect on patients who have a complete superficial palmar arch, that is, in 80-95% of cases. However, in our series, we found complete superficial palmar arches in only 67.5% of the upper limbs examined. One observation is that in the Coleman and Anson series, the superficial palmar branch of the RA anastomosed with the superficial palmar arch in 34.5% of all specimens. However in our series we found this in only 10% of all specimens. The second observation is that in the Coleman and Anson series, they did not find any superficial palmar arch anastomoses with the RA on the dorsal side, which we found in 18% of hands.

Group II. Incomplete superficial palmar arch. When the contributing arteries to the superficial arch do not anastomose or when the ulnar artery fails to reach the thumb and index finger, the arch is incomplete. This variation was found in 21.5% (Coleman and Anson) and 3.6% (Ikeda et al) of cases, with the Coleman and Anson series subdividing into four types of incomplete arch. The following classification is from the Coleman and Anson series.

Type 1. Both the RA and the ulnar artery form the superficial palmar arch but fail to anastomose. Only 3.2% belonged in this division.
Type 2. In 13.4% of specimens, the superficial arch is formed by the ulnar artery alone and does not provide any blood supply to the thumb and index finger.

Type 3. The median and ulnar arteries contribute to the arch but do not anastomose. Only 3.8% showed this pattern.

Type 4. In 1.1% of cases, the radial, ulnar and median arteries all give origin to the superficial arch but do not anastomose.

The findings of these two large studies suggest that the presence of an incomplete arch may complicate RA harvesting. In particular, they indicated that on average in 13% of patients who have RA harvesting the blood supply of the index finger and thumb will be affected by the presence of an incomplete superficial palmar arch.

In our study we found the deep palmar arch to be variable in size. The size of the superficial palmar arch was inversely proportional to that of the deep palmar arch. Coleman and Anson found a complete deep palmar arch in which the deep branch of the RA anastomosed with the deep branch of the UA in 97% of hands. Ikeda and associates found a complete deep palmar arch in 76.9% of hands. In our series we found this type of arch in 90% of hands. In contrast, in 1994, Mezzogiorno and colleagues found that the deep palmar arch was formed by the RA and UA in only 66.7% of 60 hands. In 21.7% of hands, the deep palmar arch was formed by the RA and an anastomotic branch formed a digital artery. The deep palmar arch was formed solely by the RA or the UA in 8.3% and 3.3% of cases, respectively.

In the case of the incomplete deep palmar arch (found in 10% of the hands in our study) all had complete superficial palmar arches. This implies that the thumb received its blood supply from the UA at the ulnar side and that the RA could be removed without endangering the circulation of the hand.
In 1978, Parks and colleagues\textsuperscript{219} published a study of the variations of the arterial supply of the thumb in 50 cadaver hands. They found that in 80% of hands, the arterial supply of the thumb usually came from the first palmar metacarpal artery (the first branch of the deep palmar arch of the RA). In 5% of hands, a branch of the second palmar metacarpal artery formed the main artery of the thumb. The first dorsal metacarpal artery, which is a branch of the RA at the dorsal side, was the main artery to the thumb in 15% of hands. This latter result was consistent with our finding that 18% of hands had a digital branch of the dorsal RA, which supplied the thumb and anastomosed with the superficial palmar arch.

In 1999, Olave and Prates\textsuperscript{220} reported the findings of an anatomical study of both hands in 30 cadavers. In 13.3% of the hands the deep palmar arch was formed by the RA passing through the second interosseous space, a variation we found in 6% of cases in our series. However, the significance of this variation in RA harvesting is minimal because the RA and UA both contribute blood supply to the arch.

My study is unique in that the anastomoses between the RA and UA have been documented and correlated in individual hands. The major finding from the series of 50 hands examined was that there were no cases of an incomplete superficial and deep palmar arch being present in the same hand. From an anatomical perspective, this study confirms that it is safe to remove the RA from its origin proximally to the level of the wrist distally. It should be noted, however, that in patients with coronary artery disease, vascular disease affecting the upper


extremities may be present. In 1999, Rauch and colleagues\textsuperscript{221} reviewed 66 upper extremities from 60 patients who underwent angiography prior to skin/muscle transplantation (63.6% of hands), creation of a hemodialysis fistula (6.1%), or evaluation of vascular diseases (30.3%). Classic superficial palmar arches and deep palmar arches were detected in 31.8% and 84.8% of the patients, respectively. These findings suggest that patients with coronary artery disease should be screened before RA harvesting in order to confirm the presence of a viable collateral circulation.

Thus, despite the findings of previous studies, our study demonstrated that, from an anatomical point of view, removing one artery from the arm down to the wrist level is safe in the majority of cases. There is, however, one situation in which RA harvesting may cause problems. In 10% of cases in our series — the RA gives off a superficial palmar branch and runs down to join with the superficial palmar arch from the ulnar artery. In this situation, the RA sometimes bifurcates early at a point 3–4 cm proximal to the radial styloid (superficial dorsal branch of the RA). It also may originate in the mid or proximal parts of the forearm. The superficial dorsal branch of the RA is present in about 3% of cases. This connection should not be divided because it might provide an important anastomosis between the radial and ulnar arteries. It seems that when one connection between these two arteries is well developed, the other connection will be less developed or absent.

While my results suggest the overall safety of RA harvesting it must be noted that my study suffers from two limitations. Firstly, I studied the anastomoses between the radial and ulnar arteries only at the level of the palmar arches. Therefore, while I may have designated an arch as incomplete, it may have possessed anastomotic connections at the level of the digital circulation. Secondly, even though there is always an anatomic connection between the two arterial

\textsuperscript{221} Rauch, Fischer, Achenbach, Klose and Wagner. Rofo Fortschr Geb Rontgenstr Neuen 1999; 171:207-10.
systems, such as that between the deep palmar arch of the RA and the superficial palmar arch of the UA, it is possible that these anastomoses may be insufficient. Thus, despite the presence of an anatomic collateral circulation, the blood supply may still be compromised when a RA is removed. The other possible limitation however is that the small anastomoses between the two systems may enlarge after the RA is harvested, thereby compensating for any initial reduction in the blood supply to the hand.

CONCLUSION

This chapter sought to demonstrate: 1) the feasibility, from a surgical perspective, of extracting the RA for use as a coronary bypass graft; and 2) the relative safety of RA harvesting in the face of considerable variations in the arterial anatomy of the upper limb. In particular, the discussion showed that it is important for surgeons to have a knowledge of the arterial supply and its variations over and above that of standard anatomical textbooks. Such knowledge is not only important for safety reasons but can also produce other benefits. For instance if recognized, a common variation such as a RA with a high origin can be useful in terms of being able to harvest a RA which is long enough to reconstruct two or three target coronary arteries.

One of the possible problems associated with RA harvesting is impaired hand circulation. However, the anatomical study conducted with my associates showed that the anastomoses between the superficial and deep palmar arch are complex and varied. Generally we found some degree of collateral circulation between the radial and ulnar arteries in all of the hands in the study suggesting, at least at a *gross anatomic level*, that in the majority of cases it is safe to harvest one artery from the forearm. There are two concerns: (1) some previous data showed that in some forearms and hands the ulnar artery is non-dominant and therefore unable to provide an adequate alternative blood supply; (2) even though some form of collateral circulation is usually present, in the case of an incomplete superficial or deep palmar arch, these anastomoses may be minimal. Furthermore, the degree and quality of hand collateral blood supply is not just determined by anatomical factors, but also can be affected by the presence of trauma or disease.
in the ulnar artery or the arteries in the hands and adaptation to blood flow and pressure.

In Chapters 6 and 7 I examine the efficacy of various screening devices for assessing the collateral circulation of the hand preoperatively.

One of the major concerns discussed in this chapter, and which runs through the thesis as a whole, is the question of the suitability of the RA as a bypass conduit. In this chapter I have demonstrated its suitability from the point of view of surgical anatomy. In the next three chapters, I discuss this issue in relation to the histology and histopathology of the RA.
Chapter 3
Vascular Histology and Histopathology

Introduction

The Structure of Blood Vessels

- Tunica intima
- Tunica media
- Tunica adventitia

Arteries

- Elastic artery
- Muscular artery
- Mixed artery

Histopathology of the Radial Artery

- Adaptive Intimal Thickening
- Atherosclerosis
- Medial Calcification

Summary
Introduction

As noted in my first chapter, one of the reasons that the use of radial artery (RA) for coronary artery bypass grafting (CABG) was abandoned in 1976 was the fact that evidence of concentric intimal hyperplasia was found in the RA at reoperation. Following the revival of interest in the RA for coronary artery bypass grafting in the early 1990s, there were further reports of pathology in the grafted RA. However, one of the problems with these studies was that the definitions of normal versus diseased vessels used were unclear. In this chapter then, I discuss the histology of arteries, the differences between normal and diseased vessels and the classification of the various types of arterial disease.

The Structure of Blood Vessels

The early development of blood vessels begins in the mesenchymal or mesoderm germ layer. The first stage of development occurs when a group of mesenchymal cells become arranged so as to enclose a space. These cells become endothelial cells, their edges merging with those of adjacent cells until the endothelium forms a continuous membrane. In the formation of an artery mesenchymal cells on the periphery of the developing endothelial tube become arranged so that they loosely encircle the tube. These mesenchymal cells differentiate into a type of cell which will eventually have the characteristics of a smooth muscle cell. This type of cell is generally accepted as being responsible for the production of elastin and probably other intercellular substances in the media and intima of a developing artery. The outer cells which form the adventitia resemble ordinary connective tissue cells rather than smooth muscle cells. Mature vessels, apart from precapillaries, follow a common plan of organization. Each specific type of vessel merely shows adaptations for particular purposes. Accordingly, every typical blood vessel wall consists of three layers: (1) the tunica intima (the innermost layer), (2) the tunica media (the middle layer) and (3)

the tunica adventitia. In this section, I focus specifically on the structural organization of arteries (Figure 3.1).

![Figure 3.1](image)

**Figure 3.1** Structural organization of the artery: Intima, Media and Adventitia

**Tunica intima**

The intima is defined as the region of the arterial wall from the endothelial surface of the lumen up to but not including the internal elastic lamina. An endothelial layer, resting upon a thin basement membrane, bounds the lumen. The subendothelial layer, underlying the endothelium, is composed of delicate fibroelastic tissue which is mostly longitudinal.

**Tunica media**

The internal elastic lamina which consists of a longitudinally dispersed layer of elastic fibres is generally accepted as a part of the media. It is typically a fenestrated membrane that allows substances to diffuse to and nourish cells deep in the vessel wall. The primary constituent of the tunica media is smooth muscle, which is arranged circularly. Elastic fibres are also commonly present, but occur in variable quantities. They are arranged in one or more fenestrated layers separated by alternating layers of smooth muscle cells. The outer limit of the media consists of a poorly defined condensation of the elastic tissue termed the external elastic lamina. In general the media is poorly vascularized. Thus the inner smooth muscle layers depend largely on direct diffusion from the vessel lumen for their nutritional needs. The middle portion receives its blood supply through small vessels (vasa vasorum) in the media and the outer layer is nourished by diffusion.
of nutrients from adventitial vessels. The contribution of each source depends on the thickness of the vessel. For example, blood vessels thinner than 0.5 mm have few, if any, small vessels in the media and must be nourished entirely by diffusion from the lumen or adventitial vessels. Vessels thicker than 0.5 mm, such as the thoracic aorta of large animals, usually have small vessels in the outer layers of the media.

**Tunica adventitia**

External to the media, the adventitial layer is composed of moderately compact fibro-elastic tissue whose fibres take a predominantly longitudinal (or loose spiral) course. It merges with the surrounding connective tissue. Arteries more than 1 mm in diameter have nutrient arteries, termed *vasa vasorum* (vessels of vessel). They supply and are mostly limited to the adventitia. Lymphatics are also present in the walls of larger arteries. Unmyelinated nerve fibres, known as vasomotor fibres, form networks beneath the adventitia and terminate on the smooth muscle of the media. Myelinated sensory fibres arborize in the adventitia.

**Arteries**

Arteries can be classified into three types based on the major component in the medial layer.

**Elastic artery**

The media constitutes the bulk of the wall and consists chiefly of concentrically arranged fenestrated laminae of elastin similar to the internal elastic lamina which separates the intima and media (Figure 3.2). Large arteries are

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predominantly elastic arteries, such as the aorta, however smaller arteries such as the internal thoracic artery, popliteal artery, intercostal artery and the tibial artery may contain many elastic lamellae thereby resembling larger arteries.

Figure 3.2 Elastic artery (Internal thoracic artery) There are multiple dark staining elastic lamella.

**Muscular artery**

Here the media is a fairly thick layer. It consists only one elastic lamina and mainly of circular smooth muscle fibres held together to form a cohesive whole by reticular, collagenic and delicate elastic fibres (Figure 3.3). The proportion of intercellular substance in relation to smooth muscle varies with the size of the vessel; hence the media of a small vessel is mostly smooth muscle, whereas that of a large muscular artery may contain much elastin. Examples of muscular arteries are the RA, celiac artery, and external iliac artery.
Mixed artery

This type is the intermediate form of the elastic and muscular artery such as the axillary artery, external carotid artery and common iliac artery.

Histopathology of the Radial Artery

The definitions of intimal hyperplasia and atherosclerosis used in this thesis are based on a report from the Committee on Vascular Lesions of the Council on Atherosclerosis, American Heart Association. The aim of this section is to summarize all of the definitions and define the clinical importance of these pathologies.

Adaptive intimal thickening

The arteries of all human beings normally have regions in which the intima is thicker than elsewhere. The thick regions are present from infancy are self-limited in growth and do not obstruct blood flow at any age. They are defined here to allow separation from atherosclerotic and other vascular disease. The thick

regions represent physiological adaptations of the artery to local changes in blood flow or wall tension. Adaptive intimal thickening can be classified into two patterns: (1) eccentric and (2) diffuse. However the two patterns may be contiguous and therefore cannot be clearly delineated from each other.

Eccentric thickening is a focal increase in the thickness of the intima associated with branches and orifices. At an arterial bifurcation the thickening involves about half the circumference of the parent and daughter vessels and extends for a short distance along the length of a bifurcation.

Diffuse thickening is a spread-out and often circumferential pattern of adaptive intimal thickening not clearly related to specific geometric configurations of arteries.

![Figure 3.4](image)

**Figure 3.4** Intimal hyperplasia, a. Eccentric intimal hyperplasia, b. Eccentric intimal hyperplasia at the branch of the artery (arrow), c. Diffuse intimal hyperplasia

Various terms have been used to describe intimal thickening of the eccentric type including: intimal cushion, spindle cell cushion, intimal pad, musculoelastic

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plaque, localized fibrous plaque, mucoid fibromuscular plaque, normal intimal cell mass and focal intimal hyperplasia, while the diffuse pattern is sometimes called diffuse intimal fibrosis. Many authors have not distinguished between the eccentric and diffuse patterns but have included them within general terms such as musculoelastic intimal thickening, fibromuscular intimal thickening and intimal fibromuscular hypertrophy. In this thesis I have employed the terms \textit{intimal hyperplasia} or \textit{intimal thickening}.

Even though adaptive intimal thickening is considered a \textit{normal} response to physiological stimuli, in laboratory animals, areas of adaptive intimal thickening have been found to differ functionally from adjacent regions without thickening. The turnover of endothelial cells, smooth muscle cells, and the concentrations of lipoproteins and other plasma components are greater in adaptively thickened regions of intima than in adjacent regions without thickening.

The relationship between adaptive intimal thickening and atherosclerosis is that when there are excessive levels of plasma lipoprotein lipid tends to accumulate mainly in the sections of intima with adaptive intimal thickening.

The colocalization of intimal thickening by lipids has led to the view that intimal thickening is part of the atherosclerotic process. However, if intimal thickening is accepted as a self-limited physiological response to hemodynamic forces in specific artery locations, then the development of a lesion refers only to changes that are superimposed. The hemodynamic forces cause thickening whether or not high concentrations of atherogenic lipoproteins are present. However when atherogenic plasma lipoproteins exceed critical levels, the same forces enhance lipoprotein accumulation in the same locations, leading to atheroma.

\textbf{Atherosclerosis}

Atherosclerosis is a disease of the medium and large-sized muscular arteries (e.g., the coronary, carotid arteries, and the arteries of the lower extremities), and the elastic arteries, such as the aorta and iliac vessels. The basic lesion – the atheroma or fibrofatty plaque – consists of a raised focal plaque within the intima,
having a core of lipid (mainly cholesterol, usually complexed with proteins and cholesterol esters) and a covering fibrous cap. The Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association (1995) classifies atherosclerosis into 8 types based on the histological and histochemical composition as well as the structure and ultrastructure of both the cell and matrix components of the lesions (Table 3.1).\textsuperscript{229} The composition of the 8 morphologically characteristic types of atherosclerotic lesions are described in the sequence in which they may evolve in the course of a human life. In the first three decades, the composition of the lesions is predominantly lipidic and relatively predictable. In the fourth decade and subsequently, the composition of advanced lesions becomes unpredictable because some continue to increase by mechanisms additional to lipid deposition.

Type I and II lesions, sometimes combined under the term early lesions, are generally the only ones which occur in infants and children, although they also occur in adults. Both type I and type II lesions represent small lipid deposits in the arterial intima. Type I lesions consist of the first microscopically and chemically detectable lipid deposits in the intima and cell reactions associated with such deposits. Type II lesions include those lesions generally referred to as fatty streaks, which on gross inspection may be visible as yellow-colored streaks, patches, or spots on the intimal surface of arteries. Such lesions do not obstruct or modify blood flow. Type III lesions may evolve soon after puberty and, in their composition, are intermediate between fatty streaks (type II) and atheroma (type IV). In this classification, the term advanced lesion is used as an umbrella term for lesions beyond type III. Advanced lesions of type IV are frequent from the third decade while lesions more advanced (type V-VIII) typically occur from the fourth decade of life. Destruction and deformity of a part of the intima are used to classify a lesion as advanced. In type IV, destruction of the intima is caused almost solely by mean of a mass of extracellular lipid localized deep in the intima (the lipid core); when an additional fibrous component forms it becomes

type V (Fig 3.5). Type VI is type V with a complication, for example hemorrhage, thrombosis, or erosion. In type VII, the lesion is largely calcific and in type VIII it is predominantly fibrotic.

Figure 3.5  Atherosclerosis in the radial artery a. Type V fibroatheroma demonstrated fibrous cap and calcification (Haematoxylin-eosin×20 original magnification), b. High magnification of atherosclerosis shows cholesterol cleft (Haematoxylin-eosin×40 original magnification).
### Table 3.1 Terms and cross-sectional diagrams of arteries used to designate different types of human atherosclerotic lesions in pathology


<table>
<thead>
<tr>
<th>Nomenclature and main histology</th>
<th>Sequences in progression</th>
<th>Earliest onset</th>
<th>Clinical correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I (Initial) lesion</strong></td>
<td>isolated macrophage foam cells</td>
<td>from first decade</td>
<td>clinically silent</td>
</tr>
<tr>
<td><strong>Type II (fatty streak) lesion</strong></td>
<td>mainly intracellular lipid accumulation</td>
<td>from third decade</td>
<td>clinically silent</td>
</tr>
<tr>
<td><strong>Type III (intermediate) lesion</strong></td>
<td>Type II changes &amp; small extracellular lipid pool</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type IV (atheroma) lesion</strong></td>
<td>Type II changes &amp; core of extracellular lipid</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type V (fibroatheroma) lesion</strong></td>
<td>lipid core &amp; fibrotic layer, or multiple lipid cores &amp; fibrotic layers, or mainly calcific, or mainly fibrotic</td>
<td>from fourth decade</td>
<td>clinically silent or overt</td>
</tr>
</tbody>
</table>
Type VI (complicated) lesion
Surface defect, hematoma-hemorrhage, thrombus

Medial Calcification

“Medial calcification” is synonymous with “Mockenberg’s arteriosclerosis” or “medial calcific sclerosis”. It is characterized by ring like calcifications within the media of medium-sized to small arteries of the muscular type (Figure 3.6). Although medial calcification may occur together with atherosclerosis in the same individual, or in the same vessel, the two disorders are totally distinct anatomically, clinically, and presumably etiologically. The vessels most severely affected are the femoral, tibial, radial, and ulnar arteries, and the arterial supply of the genital tract in both sexes. The pathogenesis is still obscure, but according to prevailing concepts, medial calcification is related to prolonged vasotonic influences. In animals, analogous medial calcifications can be produced by the prolonged intravascular infusion of vasoconstrictors such as epinephrine and nicotine.

Figure 3.6 Medial calcification: shows calcification within the media
Haematoxylin-eosin×20
(original magnification)

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230 Fuessl, Schalzky, Schewe, Frey and Goebel. Klin Wochenschr 1985; 63:211-6,
SUMMARY

In this chapter, I defined the terms used in histopathology of arteries: “normal”, “intimal hyperplasia”, “atherosclerosis”, and “medial calcification”. In the next chapter, I investigate the histopathology of the RA in a coronary artery disease population in order to determine whether the RA is suitable for use as a conduit for coronary artery bypass grafting.
Chapter 4

Comparative Histopathology of the Radial Artery versus the Internal Thoracic Artery and Clinical Predictors for Development of Intimal Hyperplasia and Atherosclerosis

(a) Comparative Histopathology of the Radial Artery versus the Internal Thoracic Artery

Introduction

Materials and Methods

Patients
Histopathology
Morphometric Analysis
Statistical Analysis

Results

Histopathology
Morphometric Analysis
Risk factors
Intimal hyperplasia and atherosclerosis
Medial calcification

Discussion

Histopathology
Morphometric Analysis
Prediction of Intimal Hyperplasia and Atherosclerosis

Conclusion

(b) Selection Criteria for the Radial Artery for Coronary Artery Bypass Grafting

SUMMARY
In this chapter, I present two related studies — conducted by myself and a number of colleagues — which sought to investigate the histopathology of the radial artery (RA). The chapter is divided into two sections, the first is a comparative study of the radial and internal thoracic arteries while the second focuses on an investigation of clinical risk factors for RA disease and selection criteria for the RA for coronary artery bypass grafting.

(a) Comparative Histopathology of the Radial Artery versus the Internal Thoracic Artery

Introduction

The internal thoracic artery (ITA) is generally accepted as the conduit of choice for coronary artery bypass grafting due to its biological properties, and excellent long-term graft patency. In 1990, Jacques van Son compared morphology of various arterial conduits, ITA, right gastroepiploic artery, inferior epigastric artery and RA in 17 patients (aged 15 to 85 years, mean 64 years) who died of nonvascular disease. Atherosclerosis was absent or mild in all four conduits. Intima-media thickness in the ITA and right gastroepiploic artery did not differ from that in the left anterior descending artery. However, the intima-media thickness in the RA and inferior epigastric artery was much greater than in the left anterior descending artery. In 1993, Son performed serial sections of the ITA from 11 individuals who had died of noncardiac disease. Most of the ITAs demonstrated an alternating histological pattern in the media, that of the proximal and distal segments being elastomuscular and that of the mid segment being elastic. The vessel with purely muscular media had a higher degree of intimal hyperplasia than those with an elastic or elastomuscular media.


The prevalence of atherosclerosis and the risk factors for the development of intimal disease in the RA in patients who have coronary artery disease have not been widely investigated. The aim of this study was to compare the prevalence of disease and degree of intimal disease by morphometric analyses in the RA and ITA in a group of patients in whom both arteries were harvested for coronary artery bypass grafting (CABG). Prospective population studies investigating the risk of coronary, cerebrovascular and peripheral vascular events suggest that atherosclerotic manifestations in different arterial beds have different risk factor profiles. Therefore the association between potential clinical risk factors for intimal hyperplasia and atherosclerosis of the RA was examined.

**MATERIALS AND METHODS**

**Patients**

Paired segments of RAs and ITAs were obtained from 150 patients who underwent CABG between May 1995 and October 1997. Their ages ranged from 42 to 83 years (average 66 yrs). There were 132 males (88%) and 18 females (12%). All patients underwent myocardial revascularization using ITAs and RAs. Initially, the specimens were obtained after intraluminal hydrostatic dilatation with papaverine in an attempt to maintain physiologic distension prior to formalin fixation. This was abandoned because double clamping of short arterial segments, required in this technique, produced unacceptable distortion. Even single clamping, required for surgical excision, distorted some specimens making them unsuitable for morphometry. Also, it has been shown that there is no significant difference in the combined width of the intima and media in arteries fixed in a flaccid state or at a pressure of 100 mmHg. The vessels used in this study were discarded distal segments of RA and ITA grafts which were approximately five mm to one cm long. A total of 300 RAs and ITAs were evaluated. The potential risk factors for atherosclerosis considered were: age, gender, diabetes mellitus,

---

history of cigarette smoking, hypertension, peripheral vascular disease (PVD), cerebrovascular disease (CVD) and hypercholesterolemia.

**Histopathology**

One hundred and fifty paired distal segments of RA and ITA were fixed in 4% formaldehyde solution. Multiple transverse slices of the vessels were processed to paraffin wax. Sections were cut at 5μm and all were stained with hematoxylin-eosin and Verhoeff Van Gieson’s elastin stain. The slides were examined by a pathologist blinded to the clinical data. Vessels were recorded as normal if there was no cellular or stromal tissue between the endothelium and the internal elastic lamina (Fig. 4.1). Vessels with any fibrous tissue and/or any myointimal cells between the endothelium and the internal elastic lamina were recorded as showing intimal thickening (Fig. 4.2, 4.3). Medial calcification was recorded if present. An atherosclerotic lesion was defined by the presence of intimal lipid lying free as cholesterol clefts or in aggregates of foamy macrophages (Fig. 4.4, 4.5). Any atherosclerotic lesion present was categorized according to Stary’s classification of vascular lesions (see Table 3.1).234

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Figure 4.1 Normal radial artery with characteristic single internal elastic lamina. The intima is a very thin layer consisting mainly of endothelium resting on the internal elastic lamina.

Verhoeff Van Gieson’s elastin × 20 (original magnification)

Figure 4.2 Radial artery with mild concentric non-atheromatous intimal thickening. The lumen of this large vessel is only slightly narrowed.

Verhoeff Van Gieson’s elastin × 10 (original magnification)

Figure 4.3 Internal thoracic artery showing mild non-atheromatous intimal thickening. The internal elastic lamina is focally discontinuous. The multiple elastic laminae within the media are characteristic of the internal thoracic artery.

Verhoeff Van Gieson’s elastin × 32 (original magnification)
Figure 4.4 Radial artery with severe atheromatous narrowing and focal medial calcification (black arrow). Free lipid with cholesterol clefts is present in the base of the atheromatous plaque (empty arrows).

Haematoxylin-eosin ×25 (original magnification)

Figure 4.5 Detail of an atheromatous plaque in the intima of a radial artery. Foam cells (arrow) are present with scattered narrow cholesterol clefts in a fibrous background.

Haematoxylin-eosin ×70 (original magnification)

Morphometric Analysis

For the purposes of quantitative measurement we excluded 40 pairs of specimens which were either distorted by the surgical or pathological preparation (38 patients), or, accompanied by incomplete risk factor data (2 patients). One hundred and ten pairs of arteries were suitable for morphometric analysis. The morphometric measurement of both arteries was analyzed by a Color Image Analysis System (Video Pro 32, Leading Edge Pty Ltd.). The internal elastic lamina circumference (IELC), intimal area, medial area, width of the intima and width of the media were measured. The diameter internal to the media (lumen+intima) (DLI) and the internal elastic lamina area (luminal area+intimal
area) (IEL area) were calculated (DLI = IELC/π, IEL area = IELC²/4π).

Previous investigators have suggested that the intima-to-media ratio is the most sensitive method available for grading atherosclerosis. In this study 3 methods were used to evaluate the degree of intimal thickening and atherosclerosis: (1) percentage of luminal narrowing, (2) intimal thickness index (ITI) and (3) intima-to-media ratio (IMR) (Fig. 4.6). The severity indices were calculated from the most severely diseased section of the specimens. The following formulae were used:

\[
\% \text{ of luminal narrowing} = \frac{100 \times \text{Intimal area}}{\text{Internal elastic lamina area}}
\]

\[
\text{Intimal thickness index} = \frac{\text{Intimal area}}{\text{Medial area}}
\]

\[
\text{Intima-to-media ratio} = \frac{\text{Width of intima at maximal intimal thickness}}{\text{Width of media at maximal intima thickness}}
\]

Figure 4.6 Schematic diagram depicting the indices used to evaluate the severity of intimal hyperplasia and atherosclerosis in the radial artery and the internal thoracic artery.

Morphometric measurements
1. **Circumference of internal elastic lamina** (IELC) (Internal elastic lamina separates intima from the muscular media)
2. **Medial area** – area between internal and external elastic lamina (external elastic lamina separates media from adventitia), width of media also measured.
3. **Width of intima** – the distance between the inner surface of the endothelium and the internal elastic lamina.

Calculated measurements
1. **Diameter internal to the media** (DLI) = IELC/π
2. **Internal elastic lamina area** (area of intima plus area of lumen) = IELC²/4π

Statistical methods

The difference between the histopathology and the morphometric parameters for paired specimens of RAs and ITAs were analyzed by McNemar’s test and paired t-test, respectively. A P value of less than 0.05 was considered significant.

Correlations between pairs of continuous variables were evaluated using Spearman’s correlation coefficients (rho). The comparison of the severity of intimal hyperplasia and atherosclerosis in the RA, with or without medial calcification, was evaluated by two sample t-tests.
Eight clinical risk factors for intimal hyperplasia and atherosclerosis (age, gender, smoking, diabetes, hypertension, peripheral vascular disease, cerebrovascular disease and hypercholesterolemia) of the RA and the ITA were included in stepwise linear regression analyses as independent variables. Percentage of luminal narrowing, intimal thickness index, and intima-to-media ratio were analyzed as dependent variables. For each regression model we calculated the percentage of variation in the dependent variable explained by the model. This is a standard measure of the usefulness of the model. If this percentage is high, the model can predict most of the variation in the dependent variable; if it is low, although the model may be useful, a large part of the variation in the dependent variable is explained by other factors. Logistic regression analysis was used to identify risk factors for medial calcification in RAs.

**RESULTS**

**Histopathology (n=150 paired segments)**

Intimal hyperplasia was seen in 94% of RAs and 68.7% of ITAs ($P<0.001$, McNemar's test). Atherosclerosis was found in 5.3% of RAs and 0.7% of ITAs ($P=0.04$). All of the atherosclerotic lesions were type V (fibroatheroma); pure lipid plaques were not seen. Medial calcification was found only in RAs (20/150, 13.3%).

**Morphometric Analysis (n=110 paired segments)**

Morphometric measurement showed that the DLI, IEL area, intimal area, medial area, width of the intima and width of the media were significantly greater in the RA compared with the ITA (all $P<0.001$) (Table 4.1). The means of the indices of intimal hyperplasia and atherosclerosis (percentage of luminal narrowing, ITI and IMR) in the RA were statistically higher than in the ITA (Table 4.2).
Table 4.1  Comparative morphometry of the radial and the internal thoracic arteries (n = 110 pairs)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Radial Artery</th>
<th>Internal Thoracic Artery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Mean</td>
</tr>
<tr>
<td>DLI (mm)</td>
<td>0.91-3.06</td>
<td>2.03</td>
</tr>
<tr>
<td>IEL area (mm²)</td>
<td>0.65-7.34</td>
<td>3.38</td>
</tr>
<tr>
<td>Intimal area (mm²)</td>
<td>0.15-3.30</td>
<td>0.70</td>
</tr>
<tr>
<td>Medial area (mm²)</td>
<td>0.71-5.25</td>
<td>2.80</td>
</tr>
<tr>
<td>Width of intima (mm)</td>
<td>0.054-1.63</td>
<td>0.27</td>
</tr>
<tr>
<td>Width of media (mm)</td>
<td>0.10-0.85</td>
<td>0.41</td>
</tr>
</tbody>
</table>

DLI–Diameter internal to media (lumen+intima); IEL area–Internal elastic lamina area (luminal area+intimal area); SD-Standard deviation

Table 4.2  Severity indices of intimal hyperplasia and atherosclerosis of the radial and internal thoracic arteries

<table>
<thead>
<tr>
<th>Severity indices</th>
<th>Radial Artery</th>
<th>Internal Thoracic Artery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Mean</td>
</tr>
<tr>
<td>% LN</td>
<td>6-66</td>
<td>21</td>
</tr>
<tr>
<td>ITI</td>
<td>0.06-1.71</td>
<td>0.26</td>
</tr>
<tr>
<td>IMR</td>
<td>0.09-10.90</td>
<td>0.85</td>
</tr>
</tbody>
</table>

% LN–Percentage of luminal narrowing, ITI–Intimal thickness index, IMR–Intima-to-media ratio

The correlation of the severity indices of the RA and ITA are summarized in Table 4.3. There was a weak correlation between the percentage of luminal narrowing of the RA and the ITA from the same patients (rho = 0.28, P<0.01).
Table 4.3  Correlation of the severity indices of intimal hyperplasia and atherosclerosis of the radial and internal thoracic arteries

<table>
<thead>
<tr>
<th></th>
<th>Radial artery</th>
<th>Internal thoracic artery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% LN</td>
<td>ITI</td>
</tr>
<tr>
<td>ITI</td>
<td>rho=0.67</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>P&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>IMR</td>
<td>rho = 0.56</td>
<td>rho = 0.74</td>
</tr>
<tr>
<td></td>
<td>P&lt;0.001</td>
<td>P&lt;0.01</td>
</tr>
</tbody>
</table>

% LN–Percentage of luminal narrowing, ITI–Intimal thickness index, IMR–Intima-to-media ratio

Comparisons were made between RAs with (n=14) and without (n=96) medial calcification. For each of the three indices of intimal hyperplasia and atherosclerosis there were no significant differences between the two groups (P > 0.5 for all three indices). However, the median levels of intimal hyperplasia were generally lower in the group with medial calcification (Table 4.4).

Table 4.4  Comparison of severity of intimal hyperplasia and atherosclerosis in the radial arteries with and without medial calcification

<table>
<thead>
<tr>
<th>Severity indices</th>
<th>RA without medial calcification (n=96) median</th>
<th>RA with medial calcification (n=14) median</th>
<th>P value Using Log (dep. variables)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% LN</td>
<td>18.7</td>
<td>15.1</td>
<td>0.6</td>
</tr>
<tr>
<td>ITI</td>
<td>0.21</td>
<td>0.21</td>
<td>0.6</td>
</tr>
<tr>
<td>IMR</td>
<td>0.50</td>
<td>0.44</td>
<td>0.8</td>
</tr>
</tbody>
</table>

% LN–Percentage of luminal narrowing, ITI–Intimal thickness index, IMR–Intima-to-media ratio

Risk factors (n=110 pairs)

Intimal hyperplasia and atherosclerosis

Table 4.5 summarizes the clinical features which were investigated as risk factors for intimal hyperplasia and atherosclerosis. The patient’s ages ranged from
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42 to 81 years (average 66, SD 9 yrs).

**Table 4.5**  Clinical characteristics of 110 patients

<table>
<thead>
<tr>
<th>Patients characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>98 (89.1%)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (10.9%)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>37 (33.6%)</td>
</tr>
<tr>
<td>Previous</td>
<td>69 (62.7%)</td>
</tr>
<tr>
<td>Current</td>
<td>4 (3.6%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>83 (75.5%)</td>
</tr>
<tr>
<td>Diet control</td>
<td>8 (7.3%)</td>
</tr>
<tr>
<td>Oral hypoglycemic drugs</td>
<td>17 (15.5%)</td>
</tr>
<tr>
<td>Insulin injection</td>
<td>2 (1.8%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>55 (50%)</td>
</tr>
<tr>
<td>Peripheral vascular disease (PVD)</td>
<td>19 (17.3%)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>11 (10%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>53 (48.2%)</td>
</tr>
</tbody>
</table>

The results of stepwise regression analyses on risk factors of intimal hyperplasia and atherosclerosis in RAs are shown in Table 4.6. For these analyses smoking was categorized as “never smoked” or “other” and diabetes was categorized as “none” or “diabetes” (any type). The distributions of the dependent variables were all positively skewed and better fits to the data were obtained by transforming to the logarithmic scale (base 10). PVD and a history of smoking were independently associated with log (percentage of luminal narrowing) and together explained 11.4% of its variability. Age and diabetes were independently associated with log (ITI) and explained 14.1% of ITI variability. Log (IMR) was
independently predicted by age, which explained 6.2% of variability.

Table 4.6  Radial artery: Results of stepwise linear regression analysis of dependent variables: Log (percentage of luminal narrowing of RA), Log (ITI of RA) and Log (IMR of RA)

<table>
<thead>
<tr>
<th>Variables</th>
<th>β coefficient</th>
<th>SE</th>
<th>t-ratio</th>
<th>P value</th>
<th>R Square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log₁₀ (%luminal narrowing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant = 0.952</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVD</td>
<td>0.142</td>
<td>0.051</td>
<td>2.81</td>
<td>0.006</td>
<td>0.073</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.09</td>
<td>0.040</td>
<td>2.23</td>
<td>0.03</td>
<td>0.041</td>
</tr>
<tr>
<td>Log₁₀ (ITI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant = −1.385</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.0085</td>
<td>0.002</td>
<td>3.63</td>
<td>&lt;0.001</td>
<td>0.090</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.127</td>
<td>0.050</td>
<td>2.52</td>
<td>0.01</td>
<td>0.051</td>
</tr>
<tr>
<td>Log₁₀ (IMR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant = −0.896</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.0095</td>
<td>0.004</td>
<td>2.68</td>
<td>0.009</td>
<td>0.062</td>
</tr>
</tbody>
</table>

PVD: 1= no, 2 = yes, smoker: 1=never, 2=ever, diabetes: 1=no, 2=yes

Table 4.7 shows the results of regression analyses on the risk factors of intimal hyperplasia and atherosclerosis in the ITA. Age and a history of smoking were independently associated with log (percentage of luminal narrowing) and together explained 15.0% of its variability. Smoking and age were independently associated with log (ITI), which explained 12.6% of ITI variability. Log (IMR) was independently predicted by age, explaining 5.7% of the variability.
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Table 4.7  Internal thoracic artery: Results of stepwise linear regression analysis of dependent variables: Log (percentage of luminal narrowing of ITA), Log (ITI of ITA) and Log (IMR ratio of ITA)

<table>
<thead>
<tr>
<th>Variables</th>
<th>β coefficient</th>
<th>SE</th>
<th>t-ratio</th>
<th>P value</th>
<th>R Square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log₁₀ (%luminal narrowing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>0.388</td>
<td></td>
<td></td>
<td></td>
<td>0.91</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.0067</td>
<td>0.02</td>
<td>3.74</td>
<td>&lt;0.001</td>
<td>0.059</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.102</td>
<td>0.035</td>
<td>2.90</td>
<td>0.004</td>
<td>0.059</td>
</tr>
<tr>
<td>Log₁₀ (ITI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>-1.379</td>
<td></td>
<td></td>
<td></td>
<td>0.079</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.131</td>
<td>0.036</td>
<td>3.62</td>
<td>&lt;0.001</td>
<td>0.047</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.0042</td>
<td>0.02</td>
<td>2.27</td>
<td>0.025</td>
<td>0.047</td>
</tr>
<tr>
<td>Log₁₀ (IMR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>-1.112</td>
<td></td>
<td></td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.0092</td>
<td>0.004</td>
<td>2.54</td>
<td>0.012</td>
<td>0.57</td>
</tr>
</tbody>
</table>

smoker: 1=never, 2=ever

Medial Calcification

Logistic regression was used to model medial calcification in the RA using the same eight risk factors that were employed for the evaluation of intimal hyperplasia and atherosclerosis. The only significant predictor was age ($P = 0.01$); increased age was associated with a higher probability of medial calcification. The odds ratio corresponding to a difference in age of 10 years was 2.7 (95% CI 1.2, 5.8).

DISCUSSION

Histopathology

Three arterial abnormalities were found in this study: intimal hyperplasia, atherosclerosis and medial calcification. Mild forms of intimal hyperplasia were found in the majority of conduit samples removed from patients undergoing
Comparative Histopathology and Risk Factors

CABG aged between 42 and 83 years. Intimal hyperplasia occurred more frequently in RA grafts than in ITA.

Intimal hyperplasia occurs as a consequence of physiologic stimuli, constituting an attempt by the tissue to maintain normal conditions of flow and/or wall tension. Regions of the intima with adaptive increases in thickness differ functionally from adjacent, thinner regions. As discussed in the previous chapter, excessive lipoprotein in the plasma tends to accumulate preferentially in the hyperplastic intima causing atherosclerosis.\textsuperscript{236}

In this series, the incidence of atherosclerosis in the RA was 5.3\% compared with 0.7\% in the ITA ($P = 0.04$). The true incidence of atherosclerosis in the RA was actually higher because some of the patients had severe macroscopic atherosclerosis of their RA, precluding its use as a bypass conduit. In addition, the prevalence of atherosclerosis in both the RA and the ITA was probably underestimated in our study because only the distal ends of arteries were examined and atherosclerosis is a segmental disease. In 1976, Kay et al. examined 215 ITAs from routine postmortem examinations and found more than a 25\% reduction in lumen diameter in 4.2\% of ITAs.\textsuperscript{237} No patient had more than a 50\% narrowing. Other postmortem and angiographic studies have reported an incidence of ITA atherosclerosis ranging from 2.4-5\%.\textsuperscript{238} According to the definitions and histological classification of atherosclerosis,\textsuperscript{239} we found only type

\begin{itemize}
\end{itemize}
V advanced atherosclerosis in this series. The age of the patients may explain why only advanced lesions were found.

The incidence of medial calcification (Monckeberg’s calcinosis) in the RA was 13.3% in our study. Medial calcification of an artery, even when extensive, is not necessarily associated with extensive intimal changes and the lumen of the artery is not to be compromised by the medial change. On the contrary, vessels with marked calcification often show less intimal involvement than is average for that age.\textsuperscript{240} However in our study, the RAs with medial calcification did not have less intimal hyperplasia or atherosclerosis. Monckeberg’s calcinosis is independent of, and unrelated to, the presence of atherosclerosis. However both are commonly found in patients older than 50 years and in patients with diabetes.\textsuperscript{241} Ninety four percent of patients who have had diabetes for longer than 35 years will also have medial calcification.\textsuperscript{242} Renal failure and familial amyloidosis with polyneuropathy have been associated with medial calcification.\textsuperscript{243} In our study however, age was the only risk factor for medial calcification. The effect of medial calcification on arteries used for CABG is unknown.

**Morphometric analysis**

Our morphometric analyses showed the RA to have a greater internal diameter and a thicker intima and media than the ITA. The severity indices were strongly correlated with each other and all were significantly greater in the RA than in the ITA.

\begin{footnotes}
\item[243] Everhart, Pettitt, Knowler, Rose and Bennett. Diabetologia 1988; 31:16-23.
\end{footnotes}
The percentage of luminal narrowing is a measure of the severity of intimal thickening, including atherosclerosis. The area rather than the thickness of the intima was measured to allow accurate evaluation of eccentric or irregular disease. The percentage of luminal narrowing is the most useful parameter for comparing intimal thickening in different vascular beds. However, although this parameter in the RA was statistically greater than in the ITA, this may not be clinically significant because the internal luminal diameter of the RA was significantly greater than in the ITA.

The intimal thickness index and the intima to media ratio are alternative methods of comparing intimal disease in different vascular beds. Of these two, the ITI is more accurate because it uses areas of intima and media rather than width. However, when comparing the RA and the ITA an assumption is made that any thickening of the media (the denominator in both ITI and IMR), for example, in hypertension, occurs to the same degree in both vascular beds. This assumption may not be valid. In addition, the greater thickness of the media of the RA compared with the ITA may invalidate the use of the ITI and the IMR as a comparative index in different vascular beds.

Kaufer and colleagues reported on the pathology of RAs and ITAs used as coronary artery bypass grafts. Using the IMR for grading atherosclerotic lesions, the mean RA grade was significantly greater than the mean ITA grade. However, in this study the classification of lesions was not clear, that is, whether the lesions were intimal hyperplasia or true atherosclerosis and the IMR may not have been a good indicator for comparative grading of vascular diseases. The greater thickness of the media in the RA may lead to a misleadingly low IMR compared with an ITA with the same severity of intimal disease. In my opinion the IMR should be used to compare the severity of atherosclerosis in the same


artery amongst different patients, but should not be used to compare atherosclerosis in two different arteries (e.g. the RA and the ITA). Therefore in the case of comparison of different type of arteries I prefer to use the percentage of luminal narrowing.

**Prediction of intimal hyperplasia and atherosclerosis**

Prospective studies have demonstrated that different arterial beds have different risk factors for the development of atherosclerosis. Smoking, hypercholesterolemia and hypertension are common risk factors for coronary artery disease, CVD and PVD, but these factors appear to impact differently on arteries in different parts of the body.\(^{246}\)

For example, Kay et al found that intimal thickening of the ITA correlated with age, hypertension, diabetes and PVD.\(^{247}\) Another autopsy series from Sisto and Isola in 1989 showed that only hypertension correlated with intimal thickness of the ITA in the 160 cadavers studied. Age, cigarette smoking, body mass index and diabetes were not associated with atherosclerosis.\(^{248}\)

Singh used angiography to study both ITAs in 150 patients with coronary artery disease. The incidence of atherosclerosis in ITAs was 2%. Atherosclerosis in the ITA did not appear to be influenced by age or PVD.\(^{249}\) Sons et al performed

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angiograms on 117 patients with cardiac disease. PVD and hyperlipidemia significantly increased the relative risk of atherosclerosis in the ITA.\textsuperscript{250}

Kaufer et al found that the degree of disease in the RA was related to gender, age, the presence of diabetes, aorto-iliac atherosclerosis and femoropopliteal atherosclerosis. These factors explained 60.67% of the variance ($P < 0.001$) using multivariate regression. None of the risk factors above correlated with the degree of ITA pathology.\textsuperscript{251}

In my study, when using the percentage of luminal narrowing as the dependent variable, the strongest predictors of intimal hyperplasia in the RA were PVD and cigarette smoking. When ITI was used as the dependent variable, age and diabetes were the most important factors. When the IMR was used, the strongest predictor was age. In the ITA, age and smoking were risk factors of marked luminal narrowing and elevated ITI. Age was the only significant risk factor for a high IMR. However, unlike Kaufer, we found a large amount of unexplained variation. The predictive variables analyzed here, therefore, cannot indicate precisely the risk of intimal hyperplasia and atherosclerosis.

From the regression analysis, we can predict future observations from our model. For example, from Table 4.6 we derived this following equation for prediction of the percentage of luminal narrowing and plotted the probability density function (distribution) (Fig. 4.7).

\[
\text{Log}_{10}(\text{% luminal narrowing of RA}) = 0.952 + 0.142\text{PVD} + 0.09\text{Smoker}
\]


Figure 4.7  Estimated cumulative distribution of the percentage of luminal narrowing in patient without peripheral vascular disease and who do not smoke.

We can calculate the upper limit of the percentage of luminal narrowing of the RA in patients with and without risk factors (Table 4.8). There is a 95% probability that future observation will be the same as, or lower than, the upper limit value. The best-case scenario in this instance is for patients who are non-smokers and do not have a peripheral vascular disease. The worst-case scenario is the opposite.

Table 4.8  The upper limit of the percentage of luminal narrowing of the radial artery in patients with or without peripheral vascular disease and nonsmoker or smoker.

<table>
<thead>
<tr>
<th>Upper limit of the percentage of luminal narrowing</th>
<th>Peripheral vascular disease</th>
<th>Smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>33.2</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>41.0</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>43.0</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>53.0</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
For the intimal thickness index, I derived the following equation.

\[
\log_{10}(\text{intimal thickness index of the RA}) = -1.385 + 0.0085 \text{Age} + 0.127 \text{Diabetes}
\]

Using the probability density function, we calculated the upper limit of the intimal thickness index (Table 4.9). I assume that an intimal thickness index of 0.5 is unsuitable for grafting (50% luminal narrowing predicted an intimal thickness index of 0.5 from the regression equation), then patients without diabetes must be younger than 70 years old to have a 95% probability of an index of 0.5 or less. In diabetic patients, they must younger than 57 years to have an index of 0.5 or less.

<table>
<thead>
<tr>
<th>Upper limit of intimal thickness index of RA</th>
<th>Age</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.49</td>
<td>69</td>
<td>No</td>
</tr>
<tr>
<td>0.50</td>
<td>70</td>
<td>No</td>
</tr>
<tr>
<td>0.51</td>
<td>71</td>
<td>No</td>
</tr>
<tr>
<td>0.52</td>
<td>71</td>
<td>No</td>
</tr>
<tr>
<td>0.49</td>
<td>55</td>
<td>Yes</td>
</tr>
<tr>
<td>0.50</td>
<td>56</td>
<td>Yes</td>
</tr>
<tr>
<td>0.50</td>
<td>57</td>
<td>Yes</td>
</tr>
<tr>
<td>0.52</td>
<td>58</td>
<td>Yes</td>
</tr>
</tbody>
</table>

For the ITA, the regression equation for the percentage of luminal narrowing is as following.

\[
\log_{10}(\text{% luminal narrowing of ITA}) = 0.388 + 0.007 \text{Age} + 0.102 \text{Smoker}
\]

I then calculated the upper limit of the percentage of luminal narrowing (Table 4.10). In patients who are non-smoker it is safe to use the ITA.
even if they are 79 years old because 95% of these patients will have a percentage of luminal narrowing less than 20.6. In smokers, 95% of patients who are 78 years old will have a percentage of luminal narrowing less than 25.6.

**Table 4.10** The upper limit of the percentage of luminal narrowing of the internal thoracic artery in smoker and nonsmoker in various age.

<table>
<thead>
<tr>
<th>Upper limit of percentage of luminal narrowing of ITA</th>
<th>Age</th>
<th>Smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>19.6</td>
<td>76</td>
<td>No</td>
</tr>
<tr>
<td>19.9</td>
<td>77</td>
<td>No</td>
</tr>
<tr>
<td>20.3</td>
<td>78</td>
<td>No</td>
</tr>
<tr>
<td>20.6</td>
<td>79</td>
<td>No</td>
</tr>
<tr>
<td>19.5</td>
<td>61</td>
<td>Yes</td>
</tr>
<tr>
<td>19.8</td>
<td>62</td>
<td>Yes</td>
</tr>
<tr>
<td>20.1</td>
<td>63</td>
<td>Yes</td>
</tr>
<tr>
<td>20.5</td>
<td>64</td>
<td>Yes</td>
</tr>
<tr>
<td>24.3</td>
<td>75</td>
<td>Yes</td>
</tr>
<tr>
<td>24.7</td>
<td>76</td>
<td>Yes</td>
</tr>
<tr>
<td>25.1</td>
<td>77</td>
<td>Yes</td>
</tr>
<tr>
<td>25.6</td>
<td>78</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**CONCLUSION**

The findings of this study suggest that the RA have a significantly greater prevalence of intimal hyperplasia, atherosclerosis and medial calcification than the ITA. Morphometric analyses of percentage of luminal area narrowing, ITI and IMR also led me to conclude that the RA has a significantly higher degree of intimal hyperplasia and atherosclerosis than the ITA. Despite the increased prevalence of disease in the RA compared with the internal thoracic artery, overall the severity indices for intimal hyperplasia and atherosclerosis were fairly low in
both vessels.

In terms of risk factors for disease, age, smoking, diabetes and peripheral vascular disease correlated with intimal hyperplasia and atherosclerosis in the RA and the ITA. However there was considerable unexplained variation in these predictive variables.

The left ITA is used almost exclusively as a pedicled graft to the left anterior descending artery. However the choice of the second graft varies widely amongst surgeons. In the light of the findings of this study I would advocate caution in selecting the RA in favor of the right ITA as a bypass conduit in patients who are elderly, diabetic, smoke or have peripheral vascular disease, and especially if the patient has a combination of these characteristics.
(b) Selection Criteria for the RA for Coronary Artery Bypass Grafting

INTRODUCTION

As described above, I found that, compared with the ITA, the RA is associated with a significantly higher prevalence of intimal hyperplasia, medial calcification and atherosclerosis. A major concern regarding the variability of the RA as a bypass conduit is the fact that these changes may affect the mid and long-term patency of grafts. Accordingly, I carried out a second study: 1) to identify the clinical risk factors for disease in the RA in a larger group of patients thereby establishing objective guidelines for identifying patients who are not suitable for RA grafts; and 2) to compare disease severity in the distal versus the proximal RA in order to be able to select that portion of the artery which has the least intimal disease.

METHODS

One hundred and eighty-four patients who underwent CABG were included in the study. The clinical characteristics, which were selected as potential risk factors for intimal disease, are summarized in Table 4.11. The patients’ ages ranged from 42 to 81 years (average 66.6, SD 9.1 yrs). RA segments from 184 patients were examined by histopathology and morphometry. In this study, we used only the percentage of luminal narrowing (%LN) and intimal thickness index (ITI) to evaluate the degree of intimal disease. Eighty-three paired segments of distal and proximal RA segments were compared morphometrically. For the distal and proximal RA comparisons, only the %LN was used, the other indices being unsuitable because the proximal RA segment had a larger medial area than the distal segment.
Table 4.11  Clinical characteristics of 184 patients

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>164</td>
<td>(89.1%)</td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>(10.9%)</td>
</tr>
<tr>
<td>Smokers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>54</td>
<td>(29.3%)</td>
</tr>
<tr>
<td>Previous</td>
<td>119</td>
<td>(64.7%)</td>
</tr>
<tr>
<td>Current</td>
<td>11</td>
<td>(6.0%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>135</td>
<td>(73.4%)</td>
</tr>
<tr>
<td>Diet control</td>
<td>11</td>
<td>(6.0%)</td>
</tr>
<tr>
<td>Oral hypoglycemic drugs</td>
<td>27</td>
<td>(14.7%)</td>
</tr>
<tr>
<td>Insulin injection</td>
<td>11</td>
<td>(6.0%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>98</td>
<td>(53.3%)</td>
</tr>
<tr>
<td>Aortoiliac disease</td>
<td>7</td>
<td>(3.8%)</td>
</tr>
<tr>
<td>Femoropopliteal disease</td>
<td>27</td>
<td>(14.7%)</td>
</tr>
<tr>
<td>Carotid disease</td>
<td>19</td>
<td>(17.3%)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>27</td>
<td>(14.7%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>98</td>
<td>(53.3%)</td>
</tr>
</tbody>
</table>

**Statistical Methods**

Ten potential clinical risk factors for vascular disease were included in stepwise linear regression analyses as independent variables. The %LN and the ITI were analyzed separately as dependent variables as each of these variables are severity indices of intimal hyperplasia and atherosclerosis. Due to the positively skewed distribution of both dependent variables, we transformed the data to the logarithmic scale (base 10) and used log dependent variables to analyze the data by stepwise linear regression analysis. Any association was examined by Spearman’s measure of correlation, rho. The difference between the morphometric parameters for paired specimens of distal and proximal
RAs was analyzed by the Wilcoxon signed rank test. A \( P \)-value of less than 0.05 was considered significant.

For each of the two severity indices we constructed a predictive model in order to: (1) indicate which risk factors were most strongly associated with disease; and (2) determine before surgery which RAs were unsuitable for grafting. To develop these models we used a one-sided prediction interval. In order to be confident that the RAs had acceptable severity indices, we set values of 50\% for \%LN and 0.5 for ITI as levels of serious concern. Setting the upper limit of the 95\% prediction interval equal to these values enabled us to determine clinical profiles of concern and identify a cut-off point for age of concern.

RESULTS

Of 184 distal RA segments, intimal hyperplasia and atherosclerosis were found in 92.9\% (171) and 6\% (11) of vessels, respectively (Figures 4.8A and 4.8B). There was only one entirely normal RA while one showed chronic inflammation. The percentage of luminal narrowing correlated with the ITI (Spearman’s rho = 0.68, \( P < 0.01 \)).

![Image](image1.png)  
**Figure 4.8** Both intimal hyperplasia (a) and atherosclerosis (b) may be associated with significant luminal narrowing. (a) Intimal hyperplasia (41.81\% LN, 0.53 ITI); (b) Atherosclerosis (47.13\% LN, 0.80 ITI).

Verhoeff Van Gieson’s elastin stain a) \( \times 5 \), b) \( \times 8 \) (original magnification)

LN = percentage of luminal narrowing, ITI = intimal thickness index
Medial calcification was found in 13.3% (11/83) of the distal RA segments and 14.5% (12/83) in the proximal RA segments.

Aortoiliac disease and diabetes were found to be significant ($P<0.05$) predictors of severe intimal disease for %LN, while these two risk factors along with age were significant predictors for ITI (Table 4.12). Aortoiliac disease and diabetes were independently associated with log (%LN) and together explained 14.1% of its variability. Aortoiliac disease, age and diabetes were independently associated with log (ITI), accounting for 22.5% of ITI variability. The severity indices in patients with and without aortoiliac disease are shown in table 4.13 and Figure 4.9 and 4.10.

**Table 4.12** Results of stepwise linear regression analysis of dependent variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>$\beta$ coefficient</th>
<th>SE</th>
<th>t ratio</th>
<th>$P$</th>
<th>R Square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log$_{10}$ (% luminal narrowing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant = 1.247</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortoiliac disease</td>
<td>0.257</td>
<td>0.074</td>
<td>3.47</td>
<td>0.001</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.096</td>
<td>0.032</td>
<td>3.01</td>
<td>0.003</td>
<td>0.051</td>
</tr>
<tr>
<td>Log$_{10}$ (ITI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant = –1.211</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortoiliac disease</td>
<td>0.340</td>
<td>0.078</td>
<td>4.37</td>
<td>&lt;0.001</td>
<td>0.106</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.0073</td>
<td>0.002</td>
<td>4.47</td>
<td>&lt;0.001</td>
<td>0.073</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.110</td>
<td>0.034</td>
<td>3.27</td>
<td>0.001</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Aortoiliac disease: 0 = no, 1 = yes; diabetes: 0 = no, 1 = yes
Table 4.13  Comparison of severity of intimal hyperplasia and atherosclerosis in the radial arteries in the patients with and without aortoiliac disease

<table>
<thead>
<tr>
<th>Severity indices</th>
<th>Patients without aortoiliac disease (n=177) median</th>
<th>Patients with aortoiliac disease (n=7) median</th>
</tr>
</thead>
<tbody>
<tr>
<td>% LN</td>
<td>18.6</td>
<td>35.2</td>
</tr>
<tr>
<td>ITI</td>
<td>0.21</td>
<td>0.53</td>
</tr>
</tbody>
</table>

% LN—Percentage of luminal narrowing, ITI—Intimal thickness index

Figure 4.9.  Boxplot of the Aortoiliac disease groups (no, yes) and the percentage of luminal narrowing in the distal RA segments. The boxes indicates the lower and upper quartiles and the central line is the median. The whiskers extend to the extreme values of the data, not including outliers (*) which are the values more than 1.5 times the interquartile distance from the upper and lower edges of the box and which are shown separately. The label numbers in the plot are the case number.
Figure 4.10. Boxplot of the Aortoiliac disease groups (no, yes) and the intimal thickness index in the distal RA segments. The boxes show the median and interquartile distance. The whiskers extend to the extreme values of the data, not including outliers (*) which are the values more than 1.5 times the interquartile distance from the upper and lower edges of the box and which are shown separately. The label numbers in the plot are the case number.

Morphometric analysis (Table 4.14) showed that the diameters of the lumen and the intima in the proximal versus the distal RA segments were not significantly different. However, the proximal RA had a significantly lower %LN compared with the distal RA ($P < 0.001$) (Figure 4.11a, b). In this comparison, we did not use the intimal thickness index as it can produce misleading results due to the fact that the proximal RA has a larger medial area.

There was no significant difference in the prevalence of medial calcification between the distal and proximal RA segments ($P = 1$, McNemar’s test).
Figure 4.11  The distal radial artery (a) shows moderate intimal thickening while the proximal radial artery (b) is nearly normal. (a) Distal radial artery (25.34% LN, 0.16 ITI); (b) Proximal radial artery (5.94% LN, 0.04 ITI).

Verhoeff Van Gieson’s elastin stain a) $\times 10$, b) $\times 11$ (original magnification)

LN = percentage of luminal narrowing, ITI = intimal thickness index

Table 4.14  Comparative morphometry of the distal and proximal segments of the radial artery (n = 83 pairs)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Distal Radial Artery</th>
<th>Proximal Radial Artery</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Mean</td>
<td>SD</td>
<td>Range</td>
<td>Mean</td>
</tr>
<tr>
<td>DLI (mm)</td>
<td>0.69-2.99</td>
<td>1.86</td>
<td>0.45</td>
<td>0.81-3.21</td>
<td>1.93</td>
</tr>
<tr>
<td>Intimal area (mm²)</td>
<td>0.12-2.13</td>
<td>0.59</td>
<td>0.33</td>
<td>0.09-1.62</td>
<td>0.46</td>
</tr>
<tr>
<td>Medial area (mm²)</td>
<td>0.57-5.07</td>
<td>2.67</td>
<td>0.86</td>
<td>0.24-7.43</td>
<td>3.32</td>
</tr>
<tr>
<td>% LN</td>
<td>5.82-74.58</td>
<td>21.74</td>
<td>9.85</td>
<td>3.54-73.54</td>
<td>15.74</td>
</tr>
</tbody>
</table>

DLI indicates diameter internal to media (lumen+intima), %LN indicates percentage of luminal narrowing, SD indicates standard deviation.
DISCUSSION

The RA is associated with a high incidence of intimal hyperplasia, a pathological process thought to be a major cause of graft atherosclerosis and graft failure.\textsuperscript{252} Although we found severe intimal hyperplasia, that is, hyperplasia causing luminal narrowing of more than 50%, in only 2.7% (5/184) of distal RAs and 1.2% (1/83) of proximal RAs prior to coronary bypass grafting, a large number of the RAs in our sample demonstrated some degree of intimal hyperplasia. These findings raise concerns about the possible effects of intimal disease in the RA following grafting.

In the first study the risk of intimal disease explained by the risk factors studied was low (6.2-14.1%). In contrast, Kaufer and colleagues who used IMR as a severity index RA disease found that gender, age, diabetes, aortoiliac disease and femoropopliteal atherosclerosis were the risk factors and these explained 60.67% of variance. Therefore, in the second study, I included and specified some of the risk factors which related to vascular disease such as aortoiliac, carotid and femoropopliteal disease. I used a percentage of luminal narrowing and intimal thickness index as severity indices. The risk factors in the second study were slightly different from the first. Aortoiliac disease replaced smoking and peripheral vascular disease. However they only explained 10.5-22.5% of variability. It is clear that other possible risk factors, such as genetic factors, remain unidentified.

The level of concern for intimal thickening was arbitrarily set at 50% for %LN as there is no set guideline for assessing the degree of intimal disease. The level of concern of 0.5 for ITI was derived from a regression analysis which

indicated that 50% luminal narrowing predicts an ITI of 0.5. Adopting these cut-off points, we found that the main variables associated with a risk of intimal hyperplasia were aortoiliac disease, age and diabetes. We then constructed profiles of those cases in which we could not be confident that the severity index was less than the pre-specified level of concern. For patients with aortoiliac disease for example, we found that we could not be 95% confident that the %LN was less than 50% and that the ITI was less than 0.5 (Figure 4.11). While this did not indicate that we could be certain that the %LN would be greater than 50%, it suggested that we should think carefully when considering such patients for RA grafting. For all other clinical profiles, however, we were at least 95% confident that the %LN was less than 50%. For ITI, we found that in patients aged 78 or over, even without aortoiliac disease or diabetes, we could not be (95%) confident that the ITI was less than 0.5. Furthermore, according to our analysis, in diabetic patients with no aortoiliac disease the RA should not be used in those aged over age 63.
In terms of selecting an appropriate segment of RA for grafting, our study found that the distal RA had a significantly higher degree of intimal disease than the proximal RA. Therefore, when the RA harvested is longer than required we recommend that the distal end be discarded. Although the proximal RA has a significantly wider medial area compared with the distal RA, this difference can be overcome by using topical and systemic vasodilatation. Excessive trimming of the RA can be eliminated by carefully measuring the length of the graft and preparing it before performing the distal anastomosis. Another way of avoiding this problem is to reverse the RA. The latter method allows the surgeon to perform the distal anastomosis without cutting the RA graft. When the RA is too short, an alternative option is to perform a Y or T graft with another graft such as an ITA.

CONCLUSION

The findings of the second study indicate the need for applying considerable caution in using the RA in patients with aortoiliac disease, in diabetic patients who are 63 or older, and in those aged ≥ 78 without diabetes. In terms of further minimizing the risk of intimal disease, I recommend using the proximal rather than the distal part of the RA.

SUMMARY

In this chapter I have sought to examine the variability of the RA as a bypass graft from a histopathologic perspective. In the first study discussed, the RA was found to have a significantly higher prevalence of intimal hyperplasia, atherosclerosis and medial calcification than in the internal thoracic artery. The RA also has a higher degree of intimal hyperplasia and atherosclerosis than in the
internal thoracic artery. I sought to identify the risk factors associated with the development of intimal hyperplasia and atherosclerosis in both arteries. The high prevalence and degree of intimal hyperplasia in the RA — a process associated with atherosclerosis — gave cause for concern regarding the possible effects on graft patency. Accordingly, in the second study, I sought to identify in a larger group of patients the clinical risk factors which were associated with intimal hyperplasia and atherosclerosis in the RA. The significant risk factors were aortoiliac disease, diabetes and aging, especially in a patients with a combination of risk factors. I defined the characteristics of patients for whom I am not confident that the RA is suitable for use as a conduit based on the degree of preexisting intimal hyperplasia and the clinical risk factor data. These characteristics are: patients with aortoiliac disease, diabetic patients who are 63 or older, and those aged \( \geq 78 \) without diabetes. Comparing the distal and proximal segments of the RA, the distal segment showed significantly higher degree of intimal hyperplasia. I recommend using the more proximal segment of the RA.

One limitation of this histopathology study is that we only examined the RA at the distal end. This is likely to have underestimated the incidence of focal atherosclerosis and intimal hyperplasia. In the next chapter, I describe examination of the RA by ultrasound, a technique which allows study of the whole length of the vessel.
Chapter 5

The Use of Ultrasound for Assessing the Radial Artery before Coronary Artery Bypass Grafting

(a) The Detection of Intimal Plaque and Arterial Calcification

Introduction

Patients and Methods

Patients
Ultrasound examination
Comparative study of the ultrasound and histopathology
Histopathology
Statistical Methods

Results

Calcification
Luminal diameter
Risk factors
Histopathology
Comparison between ultrasound calcification and histopathology

Discussion

Conclusion

(b) The Measurement of Intimal hyperplasia

Introduction

Patients and Methods

Results

Discussion

Conclusion

Summary
In the previous chapter, I examined the histological viability of the radial artery (RA) as a graft conduit and found that the RA has a higher rate of intimal hyperplasia, atherosclerosis and medial calcification. It therefore would be useful if a method could be found to screen patients for possible arterial disease prior to RA harvesting.

Accordingly, in this chapter I examine the efficacy of ultrasound for assessing the RA prior to coronary artery bypass grafting (CABG). The chapter is divided into two sections. In the first section I present a study examining the prevalence of intimal plaque and calcification in the RA by ultrasound and also the efficacy of ultrasound for assessing luminal diameter in the RA. In the second section I investigate whether ultrasound measurement of intima-media thickness is useful for assessing the degree of intimal hyperplasia and atherosclerosis in the RA.

(a) The Detection of Intimal Plaque and Arterial Calcification

Introduction

Intimal atherosclerosis makes an artery unusable for use as a bypass graft. We do not know the effect of medial calcification on long-term graft patency. Without the shock-absorbing capacity of a normal artery, the calcified wall may be subjected to greater shear and intramural stresses, exposing the intima to greater injury. Calcification may also limit an artery’s ability to protect itself through the mechanism of compensatory dilatation. In peripheral vessels, the presence of medial calcification increases the likelihood of ischemia and is significantly associated with severe arterial occlusive disease of the lower limbs. For these reasons, in our current surgical practice, we do not use RAs


which are heavily calcified especially when associated with poor intraoperative flow.

Another undesirable feature of any conduit is a small luminal diameter, whether caused by intimal hyperplasia or small vessel size. This potentially increases the risk of graft complications. In addition it is known that the pressure drop across an area of stenosis is related to the absolute luminal diameter. Pre-operative, non-invasive detection of RA calcification and small luminal diameter may therefore be important.

Doppler ultrasound has been widely used for investigating atherosclerosis and evaluating the progression of disease in both carotid disease and peripheral vascular disease. It has also proved to be useful and accurate for measuring the wall thickness of arteries. In this study, we used Doppler ultrasound to examine the RA before CABG. It is also useful to know which patients are prone to arterial disease and have an RA with a small luminal diameter prior to CABG. Therefore the clinical risk factors of the patients were also examined.

The aims of this study were: (1) to use ultrasound to document the prevalence of intimal plaque and arterial calcification and to identify arteries with a small luminal diameter; (2) to investigate the efficacy of ultrasound in assessing arterial calcification in the RA by comparing it to histopathology; and (3) to identify the clinical risk factors for arterial calcification and small luminal diameter radial arteries in a coronary artery patient population.


PATIENTS AND METHODS

Patients

Seventy-three patients scheduled for coronary artery bypass grafting were included in the study. Their ages ranged from 40 to 85 years (average 67.1±9.8 yrs). There were 60 males (82.2%) and 13 females (17.8%). The patients characteristics and potential risk factors for atherosclerosis considered were: age, gender, diabetes mellitus, history of cigarette smoking, hypertension, carotid disease, aortoiliac disease, femoropopliteal disease, cerebrovascular disease (CVD) and hypercholesterolemia (Table 5.1).

Table 5.1  Clinical characteristics of 73 patients

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD) yrs</td>
<td>67.1 ± 9.8</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 60 (82.2%)</td>
</tr>
<tr>
<td>Smokers</td>
<td>Never smoked 16 (21.9%)</td>
</tr>
<tr>
<td></td>
<td>Previous 50 (68.5%)</td>
</tr>
<tr>
<td></td>
<td>Current 7 (9.6%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>None 51 (69.9%)</td>
</tr>
<tr>
<td></td>
<td>Diet control 3 (4.1%)</td>
</tr>
<tr>
<td></td>
<td>Oral hypoglycemic drugs 13 (17.8%)</td>
</tr>
<tr>
<td></td>
<td>Insulin injection 6 (8.2%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>43 (58.9%)</td>
</tr>
<tr>
<td>Carotid disease</td>
<td>19 (26.0%)</td>
</tr>
<tr>
<td>Aortoiliac disease</td>
<td>6 (8.2%)</td>
</tr>
<tr>
<td>Femoropopliteal disease</td>
<td>17 (23.3%)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>11 (10%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>53 (48.2%)</td>
</tr>
</tbody>
</table>
Ultrasound examination (n=73)

Ultrasound examination was performed the day before surgery by one of two sonographers using an ATL (Advanced Technology Laboratories, Bothell, Washington), HDI (High Definition™ Imaging) 5000 system with a 10 MHz compact linear array transducer. The entire length of the RA was examined for calcification and echogenic plaques. Echogenic foci in the arterial wall with posterior acoustic shadowing were recorded as calcification. Those without posterior acoustic shadowing were recorded as echogenic plaques. Stenosis was defined as a focal increase in peak systolic velocity compared with the proximal arterial segment.

The luminal diameter is the distance between the leading edge echo from the lumen-intima interface from the near wall and the leading edge of the second bright echo, which is created by the lumen-intima interface from the far wall. Over three systolic cardiac cycles, the luminal diameter of the RA at a point 1 cm from its origin and 2 cm from the RA styloid was measured (Figure 5.1 a, b). A hypoplastic RA was defined as an artery with either a distal or proximal luminal diameter of less than 1.5 mm.

A similar examination was carried out on 10 normal volunteers by the same two sonographers on the same day and at a 7-day interval in order to confirm the reliability of the ultrasound measurements.

Figure 5.1  The ultrasound measurement of radial artery luminal diameter

a. diagram depicts a cross section of the artery demonstrating the intima, media, lumen and adventitial layers. The luminal diameter is the distance between the leading edge echo from the lumen-intima interface (brown) from the near wall and the leading edge of the second bright echo, which is created by the lumen-intima interface (brown) from the far wall.

b. ultrasound image of the distal end of the radial artery 2 cm proximal to radial styloid process demonstrating the luminal diameter.
Comparative study of ultrasound and histopathology (n=78 specimens)

Ten patients with severe RA calcification observed by ultrasound (US) were regarded as having arteries unsuitable for grafting therefore the RAs were not harvested. In one of the patients undergoing RA exploration, the RA was found to be unsuitable for use as a conduit for grafting. Fourteen other patients were excluded because their surgeons were non-compliant (7), the patients were either enrolled in other studies (5), or their operations were cancelled (2). Nine patients were excluded due to the absence of specimens. This process of elimination resulted in RA specimens from forty of the seventy-three patients being available for histopathologic examination. In one of these patients the distal RA was not able to be sampled as only the proximal part was harvested. In another patient, one proximal RA segment was not accessed leaving 78 specimens for examination by histopathology. All discarded RAs were also examined.

Histopathology

Distal and proximal segments of RA (1 cm from origin and 2 cm from RA styloid) were sampled at the time of RA harvesting. Specimens were fixed in 4% formaldehyde solution. Multiple transverse slices of the vessels were processed to paraffin wax. Sections were cut at 5μm and all were stained with hematoxylin-eosin and Verhoeff Van Gieson’s elastin stain. The slides were examined by a pathologist blinded to the ultrasound results.

Statistical methods

Ultrasound examination

A comparison of the mean diameters of the distal and proximal RA segments as measured by US was performed by paired sample t-test. Correlations between pairs of continuous variables were evaluated using Pearson correlation coefficients (r).
Intra-and inter-observer variability was estimated by calculating the difference between paired measurements according to the method of Bland and Altman. Correlation coefficients were also used. Since the data were not normally distributed, Spearman rank order correlations (rho) were used.

Ten clinical risk factors (Table 5.1) for RA plaques and calcification were included in logistic regression analyses as independent variables. A forward stepwise procedure was used to identify a suitable model. Exact logistic regression was used to fit the model to the data after the model was identified. Positive RA calcification and any RA abnormality (RA calcification or echogenic plaques) observed by US were included as dependent variables. The presence of plaques was not analyzed as a dependent variable since only 5 out of 73 patients had plaques. P values and 95% confidence intervals were reported for key results.

To identify the risk factors for hypoplasia we used the same ten risk factors, and the distal luminal diameter as a continuous independent variable, in the stepwise linear regression analysis.

**Comparison between ultrasound and histopathology**

A comparative analysis of the difference between paired dichotomous data was performed by McNemar’s test. Statistical significance was considered to be P<0.05.

Using histopathologic examination as a “gold” standard, the test characteristics of the ultrasound in detecting arterial calcification (sensitivity, specificity, positive predictive value, negative predictive value, diagnostic

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accuracy) were calculated. Confidence intervals of test characteristics for the distal and proximal RA segments’ results were obtained using the exact method.\textsuperscript{260} When the combined data were considered, confidence intervals were calculated using the bootstrap method\textsuperscript{261}, since segments from the same patient cannot be assumed to be independent.

## RESULTS

**Ultrasound examination (n=73)**

**Calcification**

RA calcification (intimal or medial) was detected by ultrasound in 24.7% (18/73) of radial arteries (Figure 5.2 a). Echogenic intimal plaques were found in 6.8% (5/73) (Figure 5.2 b). The overall incidence of RA abnormality (RA calcification or echogenic intimal plaques) was 31.5%.

\textsuperscript{260} Armitage and Berry. Statistical Methods in Medical Research 1987; Blackwell Scientific.

\textsuperscript{261} Efron and Tibshirani. An Introduction to the bootstrap 1993:168-77.
Figure 5.2 Longitudinal ultrasound images of radial artery. A, calcification with acoustic shadow. B, echogenic plaque.

Luminal diameter

The inter- and intra-observer variability of the luminal diameter of the proximal and distal segments of the RA based on data from the 10 volunteers is summarized in Table 5.2. For reliability, we require that the test have a mean difference between paired measurements which is close to zero and a small standard deviation for the differences. The “repeatability coefficient” shows the variability of the difference between the two tests. A reliable test will have a small repeatability coefficient. The repeatability coefficients ranged between 0.65 and 1.01 mm. This indicated that the difference in diameter measurement between two observations is likely to be less than 1 mm.

Table 5.2 Test-retest reliability of ultrasound measurement of the luminal diameter of the radial artery.

<table>
<thead>
<tr>
<th></th>
<th>Intra-observer variability</th>
<th>Inter-observer variability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD  rho  P</td>
<td>Mean±SD  rho  P</td>
</tr>
<tr>
<td></td>
<td>(n=10 pairs)</td>
<td>(n=10 pairs)</td>
</tr>
<tr>
<td><strong>Distal radial artery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st Mean luminal diameter</td>
<td>2.26±0.34  0.55  0.012</td>
<td>2.27±0.32  0.66  0.001</td>
</tr>
<tr>
<td>2nd Mean luminal diameter</td>
<td>2.27±0.43</td>
<td>2.27±0.44</td>
</tr>
<tr>
<td>Mean difference*</td>
<td>-0.01±0.39</td>
<td>0±0.34</td>
</tr>
<tr>
<td>Repeatability Coefficient†</td>
<td>0.74</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Proximal radial artery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st Mean luminal diameter</td>
<td>2.68±0.33  0.48  0.033</td>
<td>2.53±0.50  0.58  0.007</td>
</tr>
<tr>
<td>2nd Mean luminal diameter</td>
<td>2.59±0.54</td>
<td>2.74±0.36</td>
</tr>
<tr>
<td>Mean difference*</td>
<td>0.09±0.50</td>
<td>0.22±0.48</td>
</tr>
<tr>
<td>Repeatability Coefficient†</td>
<td>1.01</td>
<td>0.98</td>
</tr>
</tbody>
</table>

*Mean difference between paired measurements (1st and 2nd measurements)
Repeatability coefficient = \( (2.77 \times \text{estimated standard deviation of repeat observations}) \) = approximately 95% of differences between two repeated measurements will be less than the repeatability coefficient.

In the 73 patients examined by ultrasound, the luminal diameters of the distal and proximal RAs were 2.35±0.56 mm (range 1.0-3.70 mm) and 3.17±0.72 mm (range 1.13-4.60 mm), respectively (Figures 5.3, 5.4).

![Histogram of luminal diameter of the distal radial artery (mm).](image)

**Figure 5.3** The distribution of the luminal diameter of the distal radial artery (mm).
The mean proximal luminal diameter was significantly greater than that of the distal luminal diameter ($P<0.001$). The distal RA luminal diameter correlated significantly with that of the proximal luminal diameter ($r=0.51$, $P<0.001$). Hypoplasia (designated arbitrarily as a luminal diameter less than 1.5 mm; Figure 5.5) was found in 2.7% (2/73) of the distal segments and 2.7% (2/73) of the proximal segments; the two distal cases were different from the two proximal cases.

**Figure 5.4** The distribution of the luminal diameter of the proximal radial artery (mm).
Risk factors

The forward stepwise logistic procedure selected a model with the clinical risk factors of age, male gender (male worse), and carotid artery disease for RA calcification alone. Since two of these factors were of borderline significance, the logistic regression model involving all three factors was fitted to the data using an exact procedure (age: $P=0.03$, gender: $P=0.08$, carotid disease: $P=0.02$; Table 5.3).

The stepwise logistic regression procedure identified carotid disease and peripheral vascular disease as suitable risk factors for any ultrasound-detected RA disease (calcification or plaque). Using these two variables, a logistic regression was fitted to the data employing an exact procedure. The results are shown in Table 5.4. The risk factors for a small distal luminal diameter were diabetes and female gender ($P=0.002$ and 0.03, respectively).

Table 5.3 Results of exact logistic regression analysis of dependent variables for radial artery calcification
### Table 5.4 Results of exact logistic regression analysis of dependent variables for radial artery calcification and echogenic plaques

<table>
<thead>
<tr>
<th></th>
<th>$P$ value</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.03</td>
<td>2.3*</td>
<td>1.1 – 5.6</td>
</tr>
<tr>
<td>Gender</td>
<td>0.08</td>
<td>0.1</td>
<td>0.0 – 1.2</td>
</tr>
<tr>
<td>Carotid disease</td>
<td>0.02</td>
<td>5.5</td>
<td>1.3 – 27</td>
</tr>
</tbody>
</table>

* Odds ratio corresponding to an increase of 10 years.

### Histopathology (n=78 specimens)

In the proximal segments of the RA, intimal hyperplasia was found in 94.9% (37/39). Atherosclerosis was found in 2.6% (1/39). One of the proximal RA segments (2.6%; 1/39) showed chronic inflammation. Only 2.8% of the proximal RA segments (1/36) demonstrated more than 50% luminal narrowing by morphometric analysis. Three specimens were unsuitable for morphometric analysis. The proximal RA segments had slightly more medial calcification than the distal segments (20.5%; 8/39); however, this finding was not statistically significant ($P=0.73$, McNemar’s test).

Intimal hyperplasia or atherosclerosis was found in 97.4% (38/39) and 2.6% (1/39) of the distal RA segments, respectively. However, only 5.7% (2/35) of the distal RA segments demonstrated more than 50% luminal narrowing by morphometric analysis. Four specimens were unsuitable for morphometric analysis. Medial calcification was found in 15.4% (6/39) of the distal RA segments.

**Comparison between ultrasound and histopathology for detection of radial**
artery calcification (n=78 specimens)

The combined results (distal and proximal RA segments) of the comparison between ultrasound and histopathology for detection of arterial calcification are shown in Tables 5.5 and 5.6. Ten patients who demonstrated heavy diffuse RA calcification by ultrasound prior to surgery did not have RA harvesting therefore only three cases with ultrasound positive focal calcification of the proximal (1) or distal (2) RA were harvested (Fig 5.6). All three cases showed calcification histologically. When pathological calcification was present, surgical examination identified calcification in only 28.6% (2/7) for the distal RA and in 37.5% (3/8) for the proximal RA. However most of the calcification that was missed by ultrasound and by surgical examination was minimal or minor (Fig 5.7).

Table 5.5   Comparison between ultrasound and histopathology in detecting arterial calcification in the distal and proximal RA segment (n=78)

<table>
<thead>
<tr>
<th>Ultrasound Calcification</th>
<th>Histopathology Calcification</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Positive</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Negative</td>
<td>12</td>
<td>63</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>63</td>
</tr>
</tbody>
</table>
Table 5.6  Arterial calcification: ultrasound versus histopathology

<table>
<thead>
<tr>
<th>Ultrasound detection of calcification</th>
<th>Distal RA (%)</th>
<th>95% CI</th>
<th>Proximal RA (%)</th>
<th>95% CI</th>
<th>Combined (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>28.6</td>
<td>4-71</td>
<td>12.5</td>
<td>0.3-53</td>
<td>20</td>
<td>6-43</td>
</tr>
<tr>
<td>Specificity</td>
<td>100</td>
<td>89-100</td>
<td>100</td>
<td>89-100</td>
<td>100</td>
<td>*</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>100</td>
<td>16-100</td>
<td>100</td>
<td>3-100</td>
<td>100</td>
<td>*</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>86.5</td>
<td>71-96</td>
<td>81.6</td>
<td>66-92</td>
<td>84</td>
<td>73-92</td>
</tr>
<tr>
<td>Diagnostic accuracy</td>
<td>87.2</td>
<td>73-96</td>
<td>82.1</td>
<td>67-93</td>
<td>85</td>
<td>74-91</td>
</tr>
</tbody>
</table>

Confidence intervals (CI) of test characteristics for the distal and proximal RA segments by exact method. Confidence intervals of test characteristics for the combined data by the bootstrap method.

* No meaningful bootstrap confidence interval could be obtained because there was no variation in the data.

Figure 5.6 Ultrasound image of RA calcification compared with pathological examination in the same patient. In this case the calcification was moderate. Ultrasound, surgical and pathological examinations were positive for calcification.

Figure 5.7 Minor medial calcification
DISCUSSION

The prevalence of RA calcification and echogenic intimal plaques as detected by ultrasound was 25% and 7% respectively in patients with coronary artery disease who underwent CABG. This prevalence was higher than in chapter 4 which only distal portion of the RAs was examined by histopathology. This might reflect underestimation of disease in our previous chapter 4, a histopathological study, due to limited tissue sampling. There is also a tendency for more severe vasculopathic patients in our current surgical practice (Table 5.1).

Ultrasound (US) failed to detect calcification in 80% of cases (12/15, false negative rate). However, the specimens usually had only a very small amount of calcium in the histopathology sections and such a limited degree of calcification is not likely to affect graft quality. A long-term graft patency study would be required to address this issue definitively.

The specificity of US for calcification was very high, since it produced no false positive diagnoses. The other valuable measurements are the positive and negative predictive values, which combine the sensitivity and specificity with prevalence. The higher the prevalence of a disease in the population, the higher the positive predictive value and the lower the negative predictive value of the test in question. In the case of the US detection of RA calcification, the positive predictive value was calculated to be 100%, indicating that there is a 100% chance that a patient with US positive for calcification actually has RA calcification. This result may reflect the very high prevalence (25%) of calcification in this study; however, in contemporary clinical practice, there are an increasing number of patients at high risk for systemic vascular disease. In this study there was a wide range of arterial calcification from minimal to extensive calcification while the other reported severe calcification detected during the operation.262 In my study,

the negative predictive value was 84%. This means that when the US is negative, it is likely that 84% of patients do not have RA calcification.

In terms of risk factors for arterial disease, we found that age, male gender and the presence of carotid artery disease predicted RA calcification detected by US, while the risk factors associated with RA disease in general (including echogenic intimal plaques and calcification) were carotid disease and peripheral vascular disease. Note that some of these associations are of borderline statistical significance (see Table 5.3 and 5.4) but involve quite large odds ratios. The estimation of these effects, however, is imprecise due to the relatively small size of the study and the wide confidence intervals.

Another important piece of information obtained from preoperative US screening is the internal luminal diameter of the graft. From our data, we found that female patients and patients with diabetes were more likely to have smaller RAs.

In relation to the reliability of ultrasound for assessing vessel luminal diameter, our study demonstrated significant inter- and intra-observer correlations between test and retest measurement. However significant correlations do not mean that the test is reliable and in any case the observed correlations were not large. Therefore we calculated the mean and standard deviation of the difference between the two tests. The repeatability coefficient of up to 1.01 mm is relatively high. This becomes especially significant when measuring vessels less than 3 mm in diameter and may lead to clinically significant measurement error. For example, the RA in the proximal segment is large (around 3mm), so the consequence of the measurement being recorded at a value between 2 and 4 is not serious. On the other hand, for smaller luminal diameters this level of reliability may be problematic.

There were three weaknesses in this study. Firstly, using non-invasive US it is not possible to differentiate between medial calcification and calcification in the intima. It is important to distinguish between these two types because intimal calcification is associated with atherosclerosis which often leads to luminal compromise; a selection in which the artery should not be used for grafting. In contrast, medial calcification affects the media of the artery exclusively\textsuperscript{264} and the effect on graft patency remains unknown.

Secondly, we were only able to histologically examine the RA at the distal and proximal end as well as those small portions of artery left over from the operation. Accordingly, we could not confirm the presence of all echogenic intimal plaques thereby limiting the comparative power of the study.

The third problem is that in most of the patients with severe calcification on US we could not confirm the presence of calcification histologically because we did not harvest the RA in these patients. As a result, the sensitivity rate calculated for US was low. However if we assume that all 10 cases of severe calcification by US were true positives, then the sensitivity, negative predictive value and diagnostic accuracy of US is 65.7\% (23/35), 84\% (63/75) and 87.7\% (86/98), respectively. The specificity and positive predictive value remains the same at 100\%.

Is it worth screening the RA in all patients before RA harvesting? In order to determine whether or not a vessel is suitable for use as a bypass graft, the standard practice is to examine the RA visually and by palpation during surgery. Usually RAs with gross calcification are excluded. Such evaluation is subjective and likely to underestimate the degree of arterial disease present. Furthermore, compared with US, RA exploration is a highly invasive procedure and as such carries the risk of possible complications, such as paresthesia, infection and

scarring. In contrast, ultrasound is a noninvasive procedure that can be performed preoperatively. Therefore RA screening by US improves the graft selection process and may potentially improve graft patency by avoiding the use of diseased arteries. An immediate advantage to patients is the avoidance of unnecessary forearm surgery. Another benefit of ultrasound is that it can also be used to preoperatively assess the collateral circulation of the hand. It is also useful for identifying anatomical variations (e.g. the site of brachial bifurcation and diameter of the RA) as well as previous traumatic injury to the RA due to, for instance, previous catheterisation.

CONCLUSION

Although the samples were small, my results indicate that ultrasound has a high specificity for identifying RA calcification. It is also a useful diagnostic test for detecting radial arteries of small internal luminal diameter. The study also demonstrated that patients with carotid artery disease and peripheral vascular disease are at high risk of RA disease while female patients and diabetic patients are at risk of possessing radial arteries with a small internal diameter of the RA. Ultrasound has the advantage of being a non-invasive technique. Based on the findings of this study ultrasound may have a role in the preoperative assessment of RA grafts.
(b) The Measurement of Intimal Hyperplasia

Introduction

The intima-media thickness measured by ultrasound (IMT<sub>u</sub>) has been used as a noninvasive marker of atherosclerosis. These studies have demonstrated a link between intima-media thickness in the carotid artery, the prevalence of cardiovascular disease and the presence of atherosclerotic disease in other arterial beds. Also, the thickness of the intima and media of the carotid artery, as measured by ultrasound (US), is associated with an increased risk of myocardial infarction and stroke in older adults without a history of cardiovascular disease. It is therefore possible that the IMT<sub>u</sub> in the radial artery (RA) might also reflect a degree of RA intimal disease.

Accordingly, in this section I investigate the degree of correlation between the intima-media thickness complex as measured by US and the severity of intimal hyperplasia and atherosclerosis as determined by morphometric analysis from histopathology in the RAs of patients with coronary artery disease. The hypothesis is that the intima-media thickness as measured by ultrasound is useful for assessing the degree of intimal hyperplasia and atherosclerosis in the RA.

PATIENTS AND METHODS

Forty patients scheduled for coronary artery bypass grafting between July 1998 and May 1999 in whom the RA was used as one of the graft conduits were included in the study. The ultrasound (US) study was performed on the day prior to surgery. All patients with RA grafts long enough to allow a specimen to be retained were included. There was no other selection of patients in relation to patient characteristics. Their ages ranged from 40 to 80 years (mean 65.6, SD 10.5 yrs). There were 35 males (87.5%) and 5 females (12.5%). Seventy five percent of patients were smokers, 55% hypertensive, 35% diabetic, 25% had peripheral vascular disease, 22.5% carotid artery disease, 10% cerebrovascular disease, and 65% had hypercholesterolemia.

Ultrasound examination

Ultrasound examination was performed between 3-5 PM on the day before surgery in a quiet room with a stable ambient temperature of 22±3 °C by one of two sonographers using an ATL (Advanced Technology Laboratories, Bothell, Washington), HDI (High Definition™ Imaging) 5000 system with a 10 MHz compact linear array transducer. Measurements were made using electronic calipers. The US measurement method used in this study is the same as that described by Wikstrand & Wendelhag. Due to the relatively high echogenicity of the adventitia compared with the intima and media in the anterior wall, the large trailing echoes from the adventitia tend to obscure the weaker signals from the closely spaced intima. Therefore, the IMTu measurement was only taken from the far wall of the artery. The far wall intima-media thickness (IMTu) is defined as the distance between the leading edge echoes from the lumen-intima interface and the media-adventitia interface from the far wall (Figure 5.8). The IMTu of the RA was measured 1 cm from the artery’s origin and 2 cm from the radial styloid at end diastole over 3 cardiac cycles. The average of these IMTu measurements was calculated. The sonographers were blinded to the cardiovascular risk factors.

The reliability of the ultrasound measurements was investigated by performing these measurements on 10 normal volunteers. To assess the inter-observer variability, the same two sonographers in this study examined the RA twice on the same day. To assess the intra-observer variability, the sonographers performed US measurements with the same machines twice one week after the first US. The sonographers were blinded to each other’s results as well as those of the previous examination.

**Figure 5.8** Typical radio frequency (RF) signal of artery

The far wall IMT, is the distance between the leading edge echo of lumen-intima interface (orange) and the leading edge of the second bright echo from the far wall which is created by the media-adventitia interface (green).


**Histopathology**

Distal and proximal segments of RA 1 cm from the origin and 2 cm from the RA styloid were sampled at the time of harvesting. Preparation techniques were the same as those described in the previous chapter. The slides were
examined by a pathologist blinded to the ultrasound measurement.

**Morphometric Analysis**

The morphometric analysis, as outlined in the previous chapter, was performed on the RA 1 cm from the origin and 2 cm from the radial styloid (at the same sites as the US measurement). The internal elastic lamina circumference (IELC), intimal area, and medial area were measured. The internal elastic lamina area (IEL area = luminal area + intimal area) was calculated (IEL area = IELC²/4π).

Three parameters were used to assess the degree of intimal thickening and atherosclerosis: (1) the percentage of luminal narrowing (%LN); (2) the intimal thickness index (ITI); and (3) the average width of the intima-media thickness complex (IMTₘ) (Figure 5.9). The severity indices were calculated from the most severely diseased section of the specimens. The following formulae were used:

- Percentage of luminal narrowing = 100 × Intimal area / Internal elastic lamina area
- Intimal thickness index = Intimal area / Medial area
- Average width of the intima-media thickness complex = Combined width of the intima and media in eight 45-degree sectors / 8

The last parameter, the average width of the intima-media thickness complex (IMTₘ) as determined by morphometry, was measured in order to provide a direct comparison with the far wall intima-media complex thickness as measured by US (IMTₐ).
Figure 5.9  Schematic diagram depicting the histological indices used to evaluate the severity of radial artery intimal hyperplasia and atherosclerosis.

**Morphometric measurements**: Circumference of internal elastic lamina (IELC) (Internal elastic lamina separates intima from the muscular media), Intima-media complex – the distance between the intima (normally an extremely thin layer) and the external elastic lamina (external elastic lamina separates media from adventitia).

**Calculated measurements**: Internal elastic lamina area (area of intima plus area of lumen) = \( \frac{\text{IELC}^2}{4\pi} \)

**Statistical methods**

The distributions of IMT\(m\), ITI and %LN were all positively skewed and therefore transformed into the logarithmic scale (base 10) and correlated with the IMT\(u\). Correlations between pairs of continuous variables were evaluated using Pearson correlation coefficients \(r\). The factors influencing medial area were analyzed by stepwise linear regression analysis. Nine clinical risk factors for intimal hyperplasia and atherosclerosis (age, gender, smoking, diabetes, hypertension, carotid artery disease, peripheral vascular disease, cerebrovascular disease and hypercholesterolemia) were included as candidate independent variables.
Intra-and inter-observer variabilities were estimated by calculating the difference between paired measurements according to the method of Bland and Altman.

Results

Out of 40 RAs, there were four far wall ultrasound measurements missing for the distal RA and three missing for the proximal RA, therefore 36 distal and 37 proximal far wall thickness of RAs were analyzed. Due to distortion from surgical clamping, five of the distal RA specimens were unsuitable for histological morphometry and four of the proximal RA specimens were also unsuitable, therefore 35 distal and 34 proximal RA segments were analyzed by morphometric analyses. The IMT$_u$ and the severity indices for intimal hyperplasia and atherosclerosis as measured by morphometry are shown in Table 5.7.

The repeatability coefficients of the far wall intima-media complex of the proximal and distal segments of the RA are shown in Table 5.8. I regard the average repeatability coefficient of 0.35 as high.

---

Table 5.7 The far wall intima-media thickness as measured by ultrasound compared with severity indices for atherosclerosis measured by morphometry.

<table>
<thead>
<tr>
<th></th>
<th>Distal RA segments</th>
<th>Proximal RA segments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Median</td>
</tr>
<tr>
<td>Ultrasound IMTu* (mm)</td>
<td>0.37-1.75</td>
<td>0.97</td>
</tr>
<tr>
<td>Ultrasound IMTm† (mm)</td>
<td>0.34-0.88</td>
<td>0.48</td>
</tr>
<tr>
<td>Morphometry ITI‡</td>
<td>0.07-0.98</td>
<td>0.18</td>
</tr>
<tr>
<td>Morphometry %LN§</td>
<td>9.70-77.66</td>
<td>19.96</td>
</tr>
</tbody>
</table>

*IMTu = intima-media thickness measured by ultrasound.
†IMTm = intima-media thickness measured by morphometry.
‡ITI = intimal thickness index measured by morphometry.
§%LN = percentage of luminal narrowing measured by morphometry.

Table 5.8 Test-retest reliability of ultrasound measurement of far wall intima-media thickness complex

<table>
<thead>
<tr>
<th></th>
<th>Far wall intima-media thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Distal RA</td>
</tr>
<tr>
<td>Intraobserver: Repeatability Coefficient</td>
<td>0.38</td>
</tr>
<tr>
<td>Interobserver: Repeatability Coefficient</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Repeatability coefficient = \( \frac{2.77 \times \text{estimated standard deviation of repeat observations}}{g_{180}} \) = approximately 95% of differences between two repeated measurements will be less than the repeatability coefficient.

Table 5.9 shows the correlation between the IMTu and the severity indices for intimal hyperplasia and atherosclerosis as measured by morphometry. The IMTu did not correlate significantly with the Log10 IMTm, Log10 ITI, or Log10 %LN in the distal RA \( r = 0.2 \) (95%CI: -0.15 to 0.5; \( P = 0.3 \)), 0.19 (95%CI: -0.16 to 0.50; \( P = 0.3 \)) and -0.01 (95%CI: -0.35 to 0.33; \( P = 1 \)), respectively) or in the proximal RA \( r = 0.06 \) (95%CI: -0.28 to 0.39; \( P = 0.8 \)), -0.17 (95%CI: -0.47 to 0.17; \( P = 0.3 \)) and -0.11 (95%CI: -0.42 to 0.23; \( P = 0.54 \)), respectively).
In relation to the morphometry, the $\log_{10} \text{IMT}_m$ correlated moderately with $\log_{10} \%\text{LN}$ [$r = 0.48$ (95% CI, 0.19 to 0.69), $P = 0.004$] in the proximal RA segments (Table 5.10). Hence $\log_{10} \text{IMT}_m$ explained 23% of the variation in $\log_{10} \%\text{LN}$ ($r^2 = 0.23$). However no correlation was demonstrated at the distal end of RA. The $\log_{10} \text{IMT}_m$ was moderately correlated with the $\log_{10} \text{ITI}$ in both distal and proximal RA segments. [$r = 0.48$ (95% CI, 0.19 to 0.69) and 0.52 (95% CI, 0.24 to 0.72), respectively]. Thus $\log_{10} \text{IMT}_m$ explained 23% and 27% of the variation in $\log_{10} \text{ITI}$ in the distal and proximal segments of the RAs, respectively. The $\log_{10} \%\text{LN}$ correlated well with the $\log_{10} \text{ITI}$ in the distal and proximal RA segments [$r = 0.81$ (95% CI, 0.66-0.90) and 0.79 (95% CI, 0.63 to 0.88), respectively, $P < 0.001$].

The number of samples is relatively small. However, the correlations would be sensitive to outliers even if the sample was not small. More importantly, the test we have used of whether the true correlation is zero or not, depends on bivariate normality. Taking logarithms transformed the data to a scale on which the assumption of bivariate normality was reasonable. On the untransformed scale the data were too skew. The bivariate associations summarized by the correlations shown in Tables 5.9 and 5.10 were examined graphically. On the scales used, with logarithmic transformations as indicated, the assumption of bivariate normality was appropriate, as assessed by visual inspection of the relevant scatter plots. Further, in no case was there any outlier of note. Therefore, we preferred to use the more powerful test based on Pearson’s correlation, given that its assumptions are reasonably justified for these data.
Table 5.9  Correlation between far wall intima-media thickness as measured by ultrasound and severity indices (Log10 of IMT, ITI, and %LN) for atherosclerosis in the paired histopathologic sections as measured by morphometry in distal and proximal segments of the radial artery

<table>
<thead>
<tr>
<th>Variables correlated</th>
<th>Distal radial artery</th>
<th>Proximal radial artery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>r</td>
</tr>
<tr>
<td>IMTu*</td>
<td>31</td>
<td>0.20</td>
</tr>
<tr>
<td>Log10 IMTm†</td>
<td>31</td>
<td>0.19</td>
</tr>
<tr>
<td>IMTu</td>
<td>31</td>
<td>-0.01</td>
</tr>
</tbody>
</table>

*IMTu = far wall intima-media thickness measured by ultrasound.
†IMTm = average of intima-media thickness measured by morphometry.
‡ITI = intimal thickness index measured by morphometry.
§%LN = Percentage of luminal narrowing measured by morphometry.

Table 5.10  Correlation between severity indices (Log10 of %LN, ITI and IMTm) in the paired histopathologic sections as measured by morphometry in the distal and proximal segments of the radial artery

<table>
<thead>
<tr>
<th>Variables correlated</th>
<th>Distal radial artery</th>
<th>Proximal radial artery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>r</td>
</tr>
<tr>
<td>Log10 IMTm*</td>
<td>35</td>
<td>0.31</td>
</tr>
<tr>
<td>Log10(% LN)†</td>
<td>35</td>
<td>0.48</td>
</tr>
<tr>
<td>Log10 ITI‡</td>
<td>35</td>
<td>0.81</td>
</tr>
</tbody>
</table>

*IMTm = average of intima-media thickness measured by morphometry.
†% LN = Percentage of luminal narrowing measured by morphometry.
‡ITI = intimal thickness index measured by morphometry.

Discussion

The main finding of this study is that the intima-media complex thickness as measured by ultrasound (US) was not a good indicator of the severity of intimal disease in the RA. Even though it is well known that histological preparation will
cause all soft tissue to shrink by about 10%, the far wall IMT\textsubscript{u} should have some degree of correlation with the IMT\textsubscript{m}. Wong and colleagues compared the US and histology IMT in the carotid and femoral arterial segments. Histological preparation caused 2.5% shrinkage. Intraobserver reading variation was 0.7% for the histology and 5.4% for the US. US overestimated the thickness of the intima and the adventitia and underestimated the thickness of the media. For combined intima-media thickness, the differences between histology and imaging were insignificant, averaging 4% for the carotid artery and 9% for the femoral artery in the far-wall projection. In the near-wall projection, sonographic intima-media thickness was 20% less than that determined histologically. The authors concluded that ultrasonography is limited mainly by axial resolution in quantifying the dimensions of individual arterial tunica but is capable of accurately measuring far-wall intima-media thickness. Persson and colleagues measured the IMT\textsubscript{u} in vitro in 19 common carotid arteries and compared the results with the IMT measured by light microscopy. They found that those two measurements were closely correlated ($r=0.82$, $P<0.001$). Gamble and colleagues compared intima-media thickness measurement using US and histology in 27 segments of human carotid arteries in vitro and in situ in cadavers. They found that IMT\textsubscript{u} best represented the total wall thickness of intima plus media plus adventitia and not intima plus media alone. This is quite similar to my study where the IMT\textsubscript{u} was larger than that of the IMT\textsubscript{m} because of shrinkage and the measurement by US might have included the adventitia.

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In my study, in the RA, surprising and contrary to previous US in the carotid or femoral artery, the IMT_u did not correlate with the IMT_m and therefore the IMT_u could not be used to evaluate the severity of intimai disease. The high repeatability coefficient also cost a doubt on the reliability of the US measurement of IMT_u in the RA. One factor contributing to this finding may have been that the RA has a smaller diameter than that of the carotid artery making it more difficult to accurately measure the far wall intima-media thickness.

A moderate correlation between the IMT_m and the ITI in both distal and proximal RA segments was found. There was also a moderate correlation between the %LN and the IMT_m in the proximal RA segment but not in the distal segments. These findings, contrary to previous studies by others, suggest that if we are to attempt to estimate the severity of the intimal disease using US, we would need to examine several sections of the artery circumferentially.

My study had several limitations. These included a sampling error and problems with the US. Firstly, we measured the IMT_u at 1 cm from the origin and 2 cm from the RA styloid of the RA. While we attempted to perform the morphometric measurements at the same sites there is likely to have been some degree of variation in the site of the sampling. Also we selected the most severely diseased section in the morphometry for comparison. Another problem was that atherosclerosis is often a focal and eccentric disease but US often only measures one wall of the artery. It is also important that US cannot measure the width of the intima and media separately. Thus, while some factors that increase the IMT, such as hypertension, may have a disproportionate effect on the media, noninvasive US techniques conflate intimal and medial change. In the data set in the previous chapter, 184 distal segments of the RA were examined by histopathology and morphometry. Factors associated with higher media area were age and male gender. In contrast, age, patients with femoropopliteal disease or diabetes were at risk of a higher intimal area. Therefore age was the only common factor, while male sex may have an effect on the media but not on the intima. Therefore we may have overestimated the degree of intimal disease in male patients by using the IMT. Lastly, the US image sometimes makes it impossible to clearly identify
Ultrasound of the RA 173

the leading edge of the media-adventitia interface, resulting in a measurement that might not accurately reflect the intima-media thickness.

CONCLUSION

The measurement of far wall intima-media thickness by US was not useful for assessing the severity of intimal disease in the RA since it was associated with high measurement variability, and it was influenced by the thickness of the media and by the eccentric nature of intimal disease.

To accurately assess intimal disease by ultrasound we would need to: (1) overcome the technical obstacles that prevent the measurement of separate intimal and medial components of the arterial wall; (2) have an ability to examine arteries circumferential; and (3) measure at multiple sites along the length of the artery.

SUMMARY

In this chapter, I presented two studies carried out by myself and colleagues in which we examined the RA by the noninvasive ultrasound technique. In the first study we documented the prevalence of arterial calcification and hypoplasia in the RA. I identified a group of patients whose RA might not be suitable for coronary artery bypass grafting because of calcification or small luminal diameter. In the second study, I found, contrary to what was expected, that current ultrasound was not useful for assessing intimal hyperplasia in the RA. Technical advances in ultrasound would be necessary for it to be possible to accurately assess intimal disease in the RA.

In the next chapter, I compare the modified Allen test with Doppler ultrasound for the preoperative assessment of collateral circulation in the hand.
Chapter 6

Preoperative Assessment of Hand Circulation by Doppler Ultrasound and Modified Allen Test

Introduction

Patients and Methods

Study Patients
Modified Allen test
Doppler dynamic test
Statistical Methods

Results

Forearm
Hand
Comparison of Modified Allen Test and Doppler dynamic test
  Ulnar artery
  Superficial palmar branch of the radial artery
  Main thumb artery
Test characteristics for the modified Allen test
Clinical outcome

Discussion

Conclusion

Summary
INTRODUCTION

As described in Chapter 2, the blood supply to the hand typically is provided by the radial and ulnar arteries which are linked by four anastomoses. The anterior and posterior carpal arches lie adjacent to the wrist. The superficial palmar arch is primarily formed by the ulnar artery and the deep palmar arch mainly by the radial artery (RA). The latter two are the most important circuits.

The success of procedures such as RA harvesting for coronary artery bypass grafting depends upon an adequate collateral hand circulation. As my anatomical study demonstrated, there is considerable variability in the collateral blood supply to the hand. While there is usually at least one connection between the radial and ulnar artery in the hand, I found that this anastomosis can be small and may not provide an adequately supply to the hand. Furthermore, patients with coronary artery disease are at high risk of suffering from other vascular diseases such as carotid, aortoiliac disease, and peripheral vascular disease. The variability of the hand collateral blood supply, in combination with the pathology of the RA as described in Chapter 4 brought me a concern that I cannot assume that every patient will have adequate hand collateral blood supply based on anatomical study. Thus, this chapter discusses a study, carried out by me and my colleagues, of techniques for assessing the hand collateral circulation before RA harvesting.

With the resurgence of the use of the RA for coronary artery bypass grafting, tests such as the Doppler ultrasound and the Allen test have been increasingly employed as screening devices for assessing the hand collateral circulation. The Allen test was first described by Dr. Edgar V. Allen in 1929 to evaluate the patency of the arterial supply to the hand in a patient with thromboangiitis obliterans.²⁷² Originally, the test was performed on both hands simultaneously. The examiner stood at the side or in front of the patient, placing one thumb lightly over each RA, with the four fingers of each hand behind the

patient’s wrist, thus holding the wrist lightly between the thumb and fingers. The patient closed his/her hands as tightly as possible for one minute in order to squeeze the blood out of the hand while the examiner compressed each wrist between his/her thumb and fingers, thus occluding the radial arteries. The patient then quickly extended his/her fingers partially while compression of the radial arteries was maintained by the examiner. The return of color to the hand and fingers was then noted, with this recovery time theoretically reflecting the adequacy of the blood supply to the hand from the ulnar artery and its collaterals with the RA.

The Allen test has subsequently been adapted and renamed the modified Allen test,\textsuperscript{273} the primary difference between the original and the modified Allen test being that the latter is performed on one hand at a time. The fact that the modified Allen test is noninvasive and can be easily performed at the bedside has resulted, not surprisingly, in its widespread use over the years as a screening device for evaluating hand circulation. As noted, despite its popularity, its efficacy and reliability have not been proven.

Doppler ultrasound has a number of benefits as I demonstrated in Chapter 5. In relation to using the Doppler ultrasound for evaluation of hand collateral circulation, one of the drawbacks is that there are no established standard criteria for differentiating between “normal” and “abnormal” results. Several published studies have attempted to establish a standard set of criteria.\textsuperscript{274} All studies have agreed on the need for a dynamic component comparing Doppler signals with and

\textsuperscript{273} Ejrup, Fischer and Wright. Circulation 1966; 33:778-80.

without compression of the RA. However, the criteria for an “abnormal” result vary from study to study depending on which vessels are scanned.

The specific aims of this chapter, then, are: (1) to evaluate Doppler ultrasound in assessing the hand collateral circulation; (2) to establish the criteria for defining an abnormal Doppler dynamic test; and (3) to validate the modified Allen test in the assessment of hand circulation before the removal of the RA.

PATIENTS AND METHODS

Study Patients

Seventy-one patients (59 males, 12 females; mean age 67.3±9.8 years) who were eligible for coronary artery bypass grafting between July 1998 and May 1999 entered into this study. The non-dominant hands of patients were tested using both the modified Allen test and Doppler ultrasound. All observers were blinded to other results. In terms of the patients’ characteristics, 79% (56/71) were smokers including 9.9% (7/71) active smokers; 61% (43/71) were hypertensive; 31% (22 of 71) diabetic; 30% (21 of 71) had peripheral vascular disease; 27% (19/71) carotid artery disease; 13% (9/71) cerebrovascular disease; and 72% (51 of 71) had hypercholesterolemia.

Testing Methods

1) Modified Allen Test

The modified Allen test was performed according to the following protocol. The examiner faces the patient whose hand is supinated. The radial and ulnar arteries are located by their pulses. The examiner places each thumb lightly over the radial and ulnar artery simultaneously, with the four fingers of each hand placed behind the patient’s wrist thus holding the wrist lightly between the thumb and fingers. The patient’s hand is closed as tightly as possible for a period of one minute. The patient is then asked to relax the hand and extend the fingers into a slightly flexed position while the examiner maintains pressure on the radial and ulnar arteries. The hand at this point should appear blanched. The examiner then
releases the pressure on the ulnar artery and continues applying pressure to the radial artery. The return of color to the hand and fingers is noted. In our study, the recovery time was recorded as the time taken (in seconds) for the hand to return to its normal color following the release of the ulnar artery. One experienced observer performed all of the tests. An abnormal modified Allen test result was defined as a recovery time exceeding 10 seconds.

(2) **Doppler dynamic test**

Doppler US examination was performed the day before surgery by one of two sonographers using an ATL (Advanced Technology Laboratories, Bothell, Washington), HDI 5000 system with a 10 MHz compact linear array transducer. The temperature in the ultrasound laboratory was maintained between a range of 23 to 25 degrees Celsius. Patients sat comfortably on a chair with their forearms and hands positioned at the level of the heart.

Ultrasound was used to identify the bifurcation of the brachial, radial and ulnar arteries in the forearm. A high division of the brachial artery was recorded. I then examined: (1) the ulnar artery (UA) at the wrist; (2) the superficial palmar branch of the RA (SPA), arising from the distal RA on the palmar aspect; and (3) the dorsal digital thumb artery (TA), located at the medial side of the base of the thumb. The Doppler probe was placed over the expected anatomical position of the artery and aligned with it at an angle of less than 60°. By moving the probe from side to side across the vessel, the center of the artery could be located readily by a characteristic noise produced at the frequency of the pulse rate. When a steady state was achieved, the RA was firmly compressed. The peak systolic velocity of flow in the UA, SPA and TA with and without RA compression was recorded. To ensure a consistent sample volume, the sonographers attempted to keep the Doppler tracing on the same screen before and after RA compression while the peak systolic velocity was recorded.

Flow patterns in the UA were categorized into 3 groups: (1) no flow; (2) decreased flow; and (3) increased flow. Flow patterns in the SPA and TA with RA compression were categorized into 4 groups: (1) no flow; (2) decreased flow; (3)
reversed flow; and (4) increased flow.

Statistical Methods

Data analysis was carried out using SPSSPC version 10. The data were summarized in terms of a mean and standard deviation. Analysis of variance (ANOVA) was used to compare the mean differences of the recovery time by modified Allen test between the four categories of flow patterns in the SPA, UA and TA. The recovery time by modified Allen test was used as a single continuous response variable. Tests of normality were carried out and, where necessary, Box-Cox transformations were used to obtain scales for which the assumptions of the ANOVA were justified. Tukey’s multiple comparisons procedure was used to test for pair-wise differences between the flow patterns in the UA, SPA, and TA groups. Statistical significance was assumed for \( P \) values less than 0.05.

Standard estimates of sensitivity, specificity, and positive and negative predictive values were obtained by using a two-by-two contingency table.

RESULTS

Forearm

Ultrasound identified a high division of the brachial artery in 5.6% (4/71) of the patients. All of the ulnar and radial arteries were patent at the bifurcation and the elbow.

Hand

An abnormal modified Allen test was found in 5.6% (4/71) of the patients. The distribution of the flow patterns of the UA, SPA and TA is summarized in Table 6.1. In the group of three patients who had a “no flow” pattern in the UA, one had a high division of the brachial artery, one had calcification of the UA, and the other had an occluded UA at the wrist. The SPA could not be identified in five patients (7%).

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Table 6.1. The distribution flow patterns in ulnar artery (UA), superficial palmar branch of RA (SPA) and thumb artery (TA).

<table>
<thead>
<tr>
<th>Changes in peak systolic velocity with RA compression</th>
<th>UA flow pattern n (%)</th>
<th>SPA flow pattern n (%)</th>
<th>TA flow pattern n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No flow</td>
<td>3 (4.2)</td>
<td>7 (10.6)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Decreased flow</td>
<td>13 (18.3)</td>
<td>26 (39.4)</td>
<td>61 (85.9)</td>
</tr>
<tr>
<td>Reversed flow</td>
<td>0</td>
<td>18 (27.3)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Increased flow</td>
<td>55 (77.5)</td>
<td>15 (22.7)</td>
<td>6 (8.5)</td>
</tr>
<tr>
<td>Total</td>
<td>71 (100)</td>
<td>66 (100)</td>
<td>71 (100)</td>
</tr>
</tbody>
</table>

Comparison of modified Allen test and Doppler dynamic test

Ulnar artery

For UA, the data did not meet the assumptions of analysis of variance. In particular, the three groups (no flow, increased flow and decreased flow) showed significantly different variances. Box-Cox transformations were attempted to find a scale on which the assumptions of ANOVA were more satisfactorily met. For UA, the transformation used was: (Recovery time by the modified Allen test)^* = 1/(Recovery time by the modified Allen test^{0.3}); on this transformed scale Bartlett’s test for heterogeneity of variance was not significant. This gave the following ANOVA:

Table 6.2 Results of an ANOVA: Analyzing the differences among three flow patterns groups of the ulnar artery (UA).

<table>
<thead>
<tr>
<th></th>
<th>DF</th>
<th>Seq SS</th>
<th>Adj SS</th>
<th>MS</th>
<th>F</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UA</td>
<td>2</td>
<td>0.192</td>
<td>0.192</td>
<td>0.096</td>
<td>13.13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Error</td>
<td>68</td>
<td>0.496</td>
<td>0.496</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>0.688</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DF = Degree of freedom, Adj = Adjusted, SS = Sum of Squares, MS = Mean Square

Using Tukey’s method to adjust for multiple comparisons, it was found that the no flow group had Allen tests, on average, which were significantly higher.
than each of the other two groups \((P<0.001)\). There was no significant difference between the increased flow and decreased flow groups \((P>0.9)\).

**Superficial palmar branch of the radial artery**

For SPA, the same transformation (as for UA) proved to be an appropriate scale for analysis. This gave the following ANOVA (Table 6.3):

<table>
<thead>
<tr>
<th></th>
<th>DF</th>
<th>Seq SS</th>
<th>Adj SS</th>
<th>Adj MS</th>
<th>F</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPA</td>
<td>3</td>
<td>0.172</td>
<td>0.172</td>
<td>0.057</td>
<td>7.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Error</td>
<td>62</td>
<td>0.507</td>
<td>0.507</td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>65</td>
<td>0.678</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DF = Degree of freedom, Adj = Adjusted, SS = Sum of Squares, MS = Mean Square

Tukey’s multiple comparisons procedure showed that the recovery time by modified Allen test in the “no flow” group was significantly different from each of the “decreased” \((P = 0.002)\), “increased” \((P = 0.01)\) and “reversed flow” \((P < 0.001)\) groups. However, the “decreased, increased and reversed flow” groups were not significantly different from each other \((P > 0.4\) for all pair-wise comparisons).

**Main thumb artery**

For TA, the same transformation (as for UA) was used. This gave the following ANOVA (Table 6.4). The pairwise comparisons were as for UA and SPA: using Tukey’s method to adjust for multiple comparisons, it was found that the “no flow” group had Allen tests, on average, which were significantly higher than each of the “decreased” \((P < 0.001)\), “increased” \((P < 0.001)\) and “reversed flow” \((P < 0.01)\) groups, and there were no significant pairwise differences between those groups \((P > 0.4\) for all pair-wise comparison).

<table>
<thead>
<tr>
<th></th>
<th>DF</th>
<th>Seq SS</th>
<th>Adj SS</th>
<th>Adj MS</th>
<th>F</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPA</td>
<td>3</td>
<td>0.172</td>
<td>0.172</td>
<td>0.057</td>
<td>7.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Error</td>
<td>62</td>
<td>0.507</td>
<td>0.507</td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>65</td>
<td>0.678</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6.4 Results of an ANOVA: Analyzing the differences among four flow patterns groups of the main thumb artery (TA).
Test characteristics for the modified Allen test

The “no flow” pattern in the Doppler dynamic test was defined as abnormal and the others as normal. Table 6.5 shows the comparison of the modified Allen test results with the Doppler dynamic test in the UA, SPA and TA groups. Table 6.7 represents a summary of the test characteristics of the modified Allen test compared with the Doppler dynamic test.

Table 6.5 Comparison of the modified Allen test and Doppler dynamic test in the ulnar artery (UA), superficial palmar branch of RA (SPA), and dorsal digital thumb artery (TA) flow pattern groups

<table>
<thead>
<tr>
<th>Flow Pattern</th>
<th>UA flow</th>
<th>SPA flow</th>
<th>TA flow</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Allen test</td>
<td>&gt; 10 Secs</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>(recovery time)</td>
<td>0-10 Secs</td>
<td>1</td>
<td>66</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>68</td>
<td>7</td>
</tr>
</tbody>
</table>

Present = Increased, decreased and reversed flow patterns.
Table 6.7 Test characteristics of the modified Allen test compared with the Doppler dynamic test

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>UA flow</th>
<th>SPA flow</th>
<th>TA flow</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>95% CI</td>
<td>%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>66.7</td>
<td>9.4-99.2</td>
<td>28.6</td>
</tr>
<tr>
<td>Specificity</td>
<td>97.1</td>
<td>89.8-99.6</td>
<td>96.6</td>
</tr>
<tr>
<td>PPV</td>
<td>50</td>
<td>6.8-93.2</td>
<td>50</td>
</tr>
<tr>
<td>NPV</td>
<td>98.5</td>
<td>92.0-100</td>
<td>91.9</td>
</tr>
<tr>
<td>Diagnostic accuracy</td>
<td>95.8</td>
<td>88.1-99.1</td>
<td>89.4</td>
</tr>
</tbody>
</table>

UA=Ulnar artery, SPA=Superficial palmar branch of the radial artery, TA=Thumb artery, CI=Confidence interval, PPV=Positive predictive value, NPV=negative predictive value.

Clinical outcome

Among the 71 patients, 48 (67.7%) had their RAs harvested for CABG. The choice of conduit depended on the surgeon’s preference and on patient enrolment in other clinical trials. None of the patients who had RA harvesting showed signs of hand ischemia in the immediate postoperative period. All of the patients harvested had modified Allen test recovery times of less than 10 seconds. Among the three patients who demonstrated a “no flow” pattern in the UA when the RA was compressed, one patient had his RA harvested. However, this case was associated with a high origin of the RA and only the proximal two thirds of the RA was harvested. Four of seven patients who had a “no flow” pattern in the SPA had RA harvesting. None of these patients suffered from hand ischemia postoperatively. Two patients who had “no flow” patterns in the thumb artery did not have RA harvesting as they both had modified Allen test recovery times of more than 10 seconds. In three cases who had “no” flow in the UA, only one case also had “no” flow in the thumb artery and in two cases who had “no” flow in the thumb artery, only one case also had “no” flow in the UA. Therefore “no” flow in the thumb artery does not necessary predict “no” flow in the UA, vice versa.

DISCUSSION
While there has been debate about over the reliability of the modified Allen test, it has been used for assessing the hand collateral circulation with some proven efficacy.\textsuperscript{276} It also has been used as a screening test at the Austin & Repatriation Medical Centre since 1994. Between October 1994 and April 2000, a total of 1657 RAs were harvested from 1323 patients (mean age 64.4, SD 10.5 years). The cut-off point of the recovery time of the modified Allen test used in the selection of these patients for RA harvesting was 10 seconds. So far there have been no ischemic complications of the hand. However, the modified Allen test is a subjective, operator/patient-dependent test and there have been a number of reports of hand ischemia after RA intervention including RA harvesting.\textsuperscript{277} Therefore I attempted to find an objective practical method for assessing the hand collateral circulation.

This study thus also sought to evaluate the utility of Doppler ultrasound for assessing hand collateral circulation. The advantage of the Doppler ultrasound technique over other tests is that it can demonstrate the anatomy, measure the flow velocity and assess the physiologic adaptation of vessels by observing the direction of the blood flow after RA compression. However, the methods of testing and criteria for evaluation vary considerably.

In 1973, Mozersky and colleagues assessed the completeness of the superficial palmar arch in 70 normal volunteers (140 hands) by using a Doppler ultrasonic velocity detector.\textsuperscript{278} They defined the superficial palmar arch as the most distal transverse vessel in the palm. By observing the changing direction and quantity of the flow velocity when the artery was compressed, they were able to


identify a complete arch (65.7%) and an incomplete arch (34.3%). Of 140 hands, ulnar dominant collateral circulation was found in 87.1%, while a radial dominant-complete arch with good retrograde flow was found in 2.1%. Therefore, in this series, 89.2% of hands were expected to retain adequate circulation when the RAs were occluded.

Doscher and colleagues in 1983 and 1985, examined 100 asymptomatic volunteers (200 hands) with Doppler ultrasound. The superficial palmar arch was scanned at the same position as Mozersky’s study. In most instances, RA occlusion produced an increase in the ulnar to radial velocity. This finding was interpreted as a complete superficial palmar arch. When RA compression failed to produce a change in velocity, this was interpreted as an incomplete superficial palmar arch. The incidence of a physiologically incomplete superficial palmar arch in this study was 11%.

In 1976, Kamienski and Barnes used a Doppler ultrasonic velocity detector for assessing the continuity of the palmar arch. There were two criteria used for defining the continuity. Firstly, the normal arterial velocity signal was described as multiphasic with a prominent systolic component and one or more diastolic sounds. An arterial obstruction results in distal arterial velocity signals which are attenuated with a resultant decrease in the systolic component and loss of the normal diastolic sounds. Secondly, the arterial velocity is increased in response to compression of the opposite artery at the wrist in normal subjects. Using these “abnormal” criteria of Doppler ultrasound, the modified Allen test showed complete concordance with the findings by Doppler ultrasound. However, in our study the ulnar velocity was found to be decreased in 13 patients (18.3%). Of these 13 patients, 6 had RA harvesting without ischemic complications. I


therefore considered both decreasing and increasing flow velocity in the UA to be normal. These findings emphasize the importance of scanning multiple sites.

Pola and colleagues in 1996 established criteria for an abnormal Doppler dynamic test in order to determine which RAs could be harvesting.\textsuperscript{281} These criteria included patients without an increase in blood flow velocity in the UA associated with flow disappearance in the SPA during RA compression. In this study, 5.9% had an abnormal Doppler dynamic test.

Finally, in 1999 Kochi and colleagues suggested the snuffbox technique. This technique involves examining the RA in the anatomical snuffbox area using color Doppler ultrasound.\textsuperscript{282} In this study, all 10 normal volunteers demonstrated reversed flow in the RA with RA compression. However, our study was more concerned with assessing thumb artery flow and with patients who might have digital arterial diseases.

In my study, I firstly examined the bifurcation point of the brachial artery to confirm the patency of the radial and ulnar arteries in the forearm and the UA at the wrist. Next, I measured the flow velocity at three different sites: (1) the UA, in order to assess the inflow of blood supply after RA harvesting; (2) the SPA, which is the terminal branch of the RA at the palmar side; and (3) the TA, which supplies the area of the hand at most risk of ischemia after RA harvesting. The advantage of the Doppler ultrasound technique is that it can demonstrate the vessels, measure the flow velocity and assess the physiologic adaptation by observing the direction of the flow in the vessels after the RA compression. In the hand, however, the arteries are small and varied as mentioned in Chapter 2. The complex patterns of anastomoses between these arteries give rise to a wide range of responses to RA compression in the different hand arteries. This makes interpretation of results more complicated; also the small size of vessels in the


The area which was particularly difficult to scan was the SPA. Accordingly, we could not demonstrate this vessel in 7% of cases (5/71). This is consistent with the finding in anatomical dissection studies that this vessel is sometimes very small.283

In terms of the direction of blood flow with RA compression, our study showed increased flow in the UA in the majority of cases. This result indicated a functional continuity between the radial and ulnar circulation in the hand. With the RA compressed, the distal perfusion pressure of the capillary bed is reduced. This results in an increase in the pressure gradient between the UA and the capillary bed causing an increase in UA flow. The reasons for reduced or absent ulnar flow with RA compression are less clear. It is possible that other arteries such as the median and interosseous arteries take over from the RA, thereby diverting blood away from the distal UA. In order to minimize the risk of hand ischemia following RA harvesting, we considered “no flow” in the UA with RA compression as an abnormal result. Before harvesting the RA in this group, an adequate collateral blood supply should be demonstrated.

The most common flow pattern in the SPA was “decreased flow”. This can be explained by the reduced perfusion pressure beyond the point of compression of the RA, the SPA’s main source of inflow. “Increased flow” suggests the presence of a large collateral supply flowing in the same direction as the RA, whereas “reversed flow” indicates that the RA flow has been replaced by a collateral supply flowing in the opposite direction. However, regardless of the direction of the flow, blood flow was still maintained by collateral flow following RA compression, indicating continuity between the arteries in the hand. Given their potential risk of hand ischemia following RA harvesting, the group of cases of most concern are those that demonstrated a “no flow” pattern. Accordingly, we considered this as an abnormal test since it might indicate incomplete superficial and deep palmar arches. Despite this risk, in this study, four patients with “no

flow” in the SPA with RA compression had RA harvesting without hand ischemia postoperatively. “No flow” in the SPA with RA compression could also be due to the presence of balanced perfusion pressure at each end of the SPA, or a watershed effect via the deep and superficial palmar arch.

The greatest area at risk of ischemia after RA harvesting is the thumb. In our opinion, the presence of “no flow” in the TA represents an absolute contraindication for RA harvesting. Even though some collateral blood supply may develop postoperatively, this group of patients carries a very high risk of hand ischemia.

Comparing the modified Allen test with the Doppler ultrasound, the former accurately predicts the Doppler flow patterns, particularly in the TA. Even though there were only two patients in the “no flow” group of the TA, there was a highly significant correlation with the modified Allen test. Comparing the modified Allen test with the flow pattern in the TA, the false positive rate was only 2.9%. Furthermore, no patients with a normal modified Allen test had “no flow” in the TA with RA compression. Overall, this study supports the validity of the use of the modified Allen test as a primary screening test for assessing the hand collateral circulation. The Doppler ultrasound is a useful tool for assessing hands which produce an abnormal modified Allen test but have a good collateral circulation, therefore increasing the number of candidates for RA harvesting.

CONCLUSION

The absence of flow in the TA during RA compression is an absolute contraindication to RA harvesting. Absent flow in the SPA and UA is not an absolute contraindication but requires demonstration of adequate digital artery blood flow prior to RA harvesting. Doppler ultrasound of the forearm is useful to exclude patients whose ulnar artery is absent, hypoplastic or diseased.

An increased recovery time using the modified Allen test predicts absence of flow in the TA in Doppler ultrasound flow patterns, demonstrating its validity as a primary screening test. The use of the Doppler dynamic test in conjunction
with the Allen test permits the safe harvesting of some RAs in patients with a false positive abnormal modified Allen test.

In the next chapter I compare the modified Allen test with the measurement of digital systolic blood pressure via photoplethysmography to confirm the validity of the modified Allen test and define the appropriate cut-off point for the recovery time for the modified Allen test.
Chapter 7

Evaluating the Safety of Radial Artery Removal: Allen Test versus Digital Brachial Systolic Blood Pressure Index using Photoplethysmography

Introduction

Patients and Methods

Study Patients
Modified Allen test
Photoplethysmography
Statistical Methods

Results

Modified Allen test
Thumb-brachial index with radial artery occlusion
Comparison of modified Allen test and thumb-brachial index
Appropriate cut-off point of the recovery time of the modified Allen test
Clinical outcome

Discussion

Conclusion

Summary
INTRODUCTION

Currently, the methods of assessing hand circulation include the modified Allen test, Doppler ultrasound, photoplethysmography, oximetric techniques, and angiography.\textsuperscript{284} The modified Allen test is easily performed by the bedside and requires no special equipment. Accordingly it is by far the most commonly used procedure for assessing the circulation of the hand. Despite its widespread use, there have been few attempts to systematically study the efficacy of the modified Allen test such a study was described in Chapter 6 and also there was a difference in the cut-off point for the modified Allen test recovery time. Photoplethysmography is a precise and proven method for recording the pulse wave and blood pressure in the fingers.\textsuperscript{285}

The first purpose of this study was to compare the accuracy of the modified Allen test with the thumb-brachial systolic blood pressure indices using photoplethysmography in the assessment of hand circulation before the removal of the radial artery (RA). The second aim was to define the appropriate cut-off point for the modified Allen test recovery time.


PATIENTS AND METHODS

Study Patients

Eighty-four patients (70 males, 14 females; mean age 65.99±9.73 years) who were eligible for coronary artery bypass grafting were entered into this study. In 79 patients the left hand, and in 75 patients the right hand, were tested using both the modified Allen test and photoplethysmography.

Testing Methods

(1) Modified Allen Test

The modified Allen test was performed similar as described in Chapter 6 and was performed by one experienced observer.

(2) Photoplethysmography

Systolic blood pressures were measured using a digital blood pressure cuff with a photoplethysmography amplifier module (PPG 100A) using the BIOPAC System Inc.’s TSD100 photoelectric plethysmogram transducer. Blood pressure analyses were obtained using the AcqKnowledge® III software and the MP100WSW (manufactured by BIOPAC Systems, Inc. 275 South Orange Ave, California). Brachial blood pressure measurement was performed using a blood pressure cuff inflated over the upper arm and a transducer secured over the brachial artery to detect the return of blood flow on deflation of the cuff. For thumb blood pressure measurements, blood pressure cuffs of 20mm in width were inflated over the thumb, while transducers secured to the volar surface of the distal phalanx were used to measure blood pressure.

Vascular assessment of the hand was performed in a laboratory and a temperature of between 23 to 25 degrees Celsius was maintained. Patients were positioned to lie comfortably on a bed with the upper body angled at 45 to 60 degrees from the horizontal. The forearm undergoing testing was rested on a table at or slightly above the level of the heart. Prior to the commencement of testing the patient’s systolic blood pressure was recorded. This was repeated at
five-minute intervals. When the systolic blood pressure returned to within 5 mmHg of the previous recording a steady state condition was considered to have been achieved and testing commenced. In order to minimize fluctuations in central blood pressure, patients were encouraged to remain relaxed and not to speak or move during data collection.

The brachial and thumb systolic blood pressures were recorded at rest. Occlusive clamps were then applied to the RA near its origin distal to the elbow and about 3cm proximal to the wrist. Doppler ultrasound was used to confirm the completeness of occlusion of the distal and proximal segments of the RA, and to verify that the clamps were not occluding other vessels. The brachial and thumb systolic blood pressures were recorded sequentially. The thumb-brachial index with RA occlusion (TBIO) was also calculated (TBIO = systolic blood pressure of thumb artery with RA occlusion/ brachial systolic blood pressure). In our study we used a thumb-brachial index rather than the index finger-brachial index because the RA contributes more to the blood supply of the thumb than to the index finger. Abnormal thumb-brachial indices were defined as those less than 0.75.

**Statistical Methods**

Data analysis was carried out using MINITAB version 12 PC and SPSSPC version 8. The data were summarized in terms of a mean and standard deviation. An analysis of thumb-brachial indices was performed by analysis of variance (ANOVA). The three categorical explanatory variables (factors) were the recovery time from the modified Allen test, the hand (right or left) tested, and factors relating to the individual patient. Hand and individual patient variables were factored into the analyses in order to accurately assess the impact of the modified Allen test factor. Recovery time from the modified Allen test was divided into three groups: (1) less than or equal to 10 seconds, (2) 11 to 20 seconds, and (3) greater than 20 seconds.

The TBIO was used as a single continuous response variable. Tests of normality were carried out and, where necessary, transformations were used to
obtain scales for which the assumptions of ANOVA were justified. Tukey’s multiple comparisons procedure was used to test for pair-wise differences among the three modified Allen test groups. Correlation between the TBIO and the modified Allen test was performed by Spearman’s correlation. Statistical significance was assumed for $P$ values less than 0.05.

**RESULTS**

**Modified Allen Test**

The distribution of the modified Allen test categories across the three groups is shown in Table 7.1. Among the 154 hands, most (107, 69.5%) had a recovery time by modified Allen test of less than or equal to 10 seconds. The modified Allen test weakly correlated with age in the right hand (Spearman’s rho=0.27, $P$ =0.02) and the left hand (Spearman’s rho = 0.38, $P$ = 0.001).

<table>
<thead>
<tr>
<th>Modified Allen test groups (recovery time)</th>
<th>Number of hands (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (0-10 seconds)</td>
<td>107 (69.5)</td>
</tr>
<tr>
<td>2 (11-20 seconds)</td>
<td>14 (9.1)</td>
</tr>
<tr>
<td>3 (&gt; 20 seconds)</td>
<td>33 (21.4)</td>
</tr>
</tbody>
</table>

**Thumb-brachial index with radial artery occlusion**

The thumb-brachial indices data are summarized in Table 7.2. The distribution of response variables (TBIO) is shown in Figure 7.1. The TBIO was ≤ 0.75 in 34 hands (22.1%).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBI</td>
<td>0.98 (0.11)</td>
<td>0.99</td>
<td>0.65</td>
<td>1.31</td>
</tr>
<tr>
<td>TBIO</td>
<td>0.87 (0.25)</td>
<td>0.94</td>
<td>0</td>
<td>1.31</td>
</tr>
</tbody>
</table>

TBI indicates thumb-brachial index; and TBIO, thumb-brachial index with RA occlusion
Comparison of Modified Allen Test and Thumb Brachial Index with Radial Artery Occlusion

There was a moderate correlation between the recovery time from the modified Allen test and the TBIO in both left and right hands (Table 7.3).

<table>
<thead>
<tr>
<th>Hand</th>
<th>Variables</th>
<th>N</th>
<th>rho</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>Modified Allen test</td>
<td>75</td>
<td>-0.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left</td>
<td>Modified Allen test</td>
<td>79</td>
<td>-0.51</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

TBIO indicates thumb-brachial index with radial artery occlusion.

After adjustment for patient and hand factors, there was a significant difference among the modified Allen test groups for TBIO (F = 6.5, P = 0.003; Table 7.4). Tukey’s multiple comparisons procedure showed that Groups 2 and 3
had significantly lower TBIO levels than Group 1 ($P = 0.01$ and $P = 0.02$ respectively), but Groups 2 and 3 were not significantly different ($P > 0.9$).

**Table 7.4** Results of analysis of variance for thumb-brachial index with radial artery occlusion (TBIO)

<table>
<thead>
<tr>
<th>Source</th>
<th>DF</th>
<th>SS</th>
<th>Adj MS</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject</td>
<td>83</td>
<td>8.57</td>
<td>0.06</td>
<td>2.19</td>
<td>0.001</td>
</tr>
<tr>
<td>Hand</td>
<td>1</td>
<td>0.03</td>
<td>0.03</td>
<td>0.57</td>
<td>0.453</td>
</tr>
<tr>
<td>Allen</td>
<td>2</td>
<td>0.61</td>
<td>0.31</td>
<td>6.47</td>
<td>0.003</td>
</tr>
<tr>
<td>Error</td>
<td>67</td>
<td>3.16</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>153*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hand indicates right or left hand; and Allen, the three categories of recovery time from the modified Allen test.

df, degrees of freedom; SS, sum of squares; Adj MS, adjusted mean square; F, ratio of mean squares.

*One outlier excluded from results.

The group of hands that had a recovery time of more than 10 seconds in the modified Allen test had a mean and median TBIO of 0.67 and 0.70 respectively (Fig. 7.2).

**Figure 7.2** Boxplot of the Allen groups (normal ≤10 seconds, abnormal >10 seconds) and thumb-brachial index with radial artery occlusion (TBIO). The boxes show the median and interquartile distance. The whiskers extend to the extreme values of the data, not including outliers (*) which are the values more than 1.5 times the interquartile distance from the upper and lower edges of the box and which are shown separately.

Defining an abnormal recovery time of the modified Allen test as more than 10 seconds and abnormal TBIO as less than 0.75, the false positive, false negative rate and diagnostic accuracy of the modified Allen test were 17%, 21%, and 82% respectively, using TBIO as a gold standard. Of the set of hand measurements for which the TBIO was ≥ 0.75, twenty-one measurements (44.7%) had an abnormal modified Allen test (Table 7.5).

**Table 7.5** Results of the modified Allen test groups compared with the thumb-brachial index with radial artery occlusion (n=154)

| Modified Allen test | Thumb-brachial index with radial artery occlusion |
Modified Allen Test and Digital Thumb Pressure Index

<table>
<thead>
<tr>
<th></th>
<th>Abnormal (&lt; 0.75)</th>
<th>Normal (≥ 0.75)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal (&gt; 10 seconds)</td>
<td>26</td>
<td>21†</td>
<td>47</td>
</tr>
<tr>
<td>Normal (≤ 10 seconds)</td>
<td>7*</td>
<td>100</td>
<td>107</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>121</td>
<td>154</td>
</tr>
</tbody>
</table>

*False negative, †False positive; based on the thumb-brachial index with radial artery occlusion.

**Appropriate cut-off point of the recovery time of the modified Allen test**

When a TBIO greater than or equal to 0.75 was defined as normal, the probability of a false positive was 21 out of 121 hands, or 17.4%. The probability of a false negative using the modified Allen test was estimated to be 7 out of 33 hands (21.2%). The most desirable test is one that has both a low false positive and a low false negative rate. Taking the false positive and the false negative rate into account simultaneously and giving them equal weight, the best measure of the accuracy of the Allen test is Youden’s misclassification index.286

Youden’s index = 100 - [false positive rate (%) + false negative rate (%)]

Using this measure, the best cut-off point for the modified Allen test time is 12 seconds, as demonstrated in the receiver operating characteristics (ROC) curve (figure 7.3). At this point, both the sensitivity and specificity estimates are high (79% and 84%, respectively), and Youden’s index achieves its maximum value of 63%.

![Figure 7.3](image-url) The receiver operating characteristic (ROC) curve. In this plot the cut-off in seconds varies from a low of 2 seconds at the top right hand corner to a maximum of 25 seconds at the bottom left hand corner. The intersection of the diagonal line and the curved plotted line provides an objective cut-off point.

If we are to rely on the modified Allen test as a screening procedure however, it is important to reduce the false negative rate and thus the number of patients at risk of hand ischemia. Therefore we will need to reduce the threshold recovery time used to determine abnormality. From our data we can generate the plot between the false negative rate and modified Allen test recovery time. The false negative rate can be estimated to be 12.1%, 15.2% and 18.2 % if we reduce the threshold recovery time from the modified Allen test to 3, 4 and 5 - 8 seconds respectively. The false negative rate increases to 21.2% when we use 9 - 12 seconds as a cut-off point (figure 7.4).

![Figure 7.4](image)

Figure 7.4 Plot of the false negative rate (%) versus the cut-off point of the recovery time for the modified Allen test (seconds).

To reduce the false negative rate to around 15-18%, it would be necessary to use a cut-off point of four to eight seconds. For the threshold of eight seconds, the sensitivity was estimated to be 82%, the specificity 80% and Youden’s index was 62% (Figure 7.5).

![Figure 7.5](image)

Figure 7.5 Plot of Youden’s index (%) versus the cut-off point of the recovery time for the modified Allen test (seconds).

**Clinical outcome**

Among the 84 patients, 36 patients had single RAs harvested and six patients had bilateral RAs harvested. The average recovery time using the modified Allen test in patients who had RA harvesting was 6.6±14.1 seconds (mean ± SD) while the average TBIO was 0.96 ± 0.20 (mean ± SD). All patients who had RA harvesting had normal Allen test (recovery time of the Allen test equal to or less than 10 seconds). Interestingly, one patient had a TBIO of 0.3 and recovery time by Allen test of 3 seconds and did not suffer from postoperative
hand ischemia. This may relate to the TBIO test error. To date, no cases of hand ischemia have occurred in these patients.

DISCUSSION

Being the simplest screening tool, the modified Allen test’s advantages are that it is easy to perform, repeatable, and does not require any instruments. Obviously, the results will be unreliable, if the Allen test is performed incorrectly.\textsuperscript{287} For example, the test may produce a falsely positive result if the hand is hyperextended. Moreover, if the RA is compressed too firmly it may cause partial compression to the ulnar artery by shearing stress thereby confounding the results.

There have been few attempts to systematically study the efficacy of the modified Allen test when performed correctly. Benit and colleagues performed modified Allen tests on 1,000 consecutive patients undergoing cardiac catheterisation.\textsuperscript{288} The times to recovery were less than 5 seconds in 49\% of patients, between 5 to 9 seconds in 24\%, and 10 seconds or more in 27\% of cases. Defining an abnormal recovery time as greater than 10 seconds, the authors noted the relatively high proportion of patients in their sample who were contraindicated for the procedure of transradial coronary angioplasty.

Hosokawa and colleagues examined 2,940 arms in patients who underwent surgery or had an examination in the anaesthesiology department. In this study, an abnormal Allen test was defined by a recovery time of more than 5 seconds.\textsuperscript{289} The Allen test showed abnormalities in 3.6\% of cases. A significant finding in this


study was that the incidence of an abnormal Allen test increased with age. The incidence was 2.2% in the first decade rising to 6.9% in the ninth decade and later. In contrast, our study showed only a weak correlation between the modified Allen test and age, which may be due to the fact that our patient population did not include young patients (with a mean age of around 66 years).

Johnson and associates used the modified Allen test in combination with pulse oximetry to assess the adequacy of the collateral circulation of the hand. They arbitrarily chose a recovery time of 12 seconds. On the basis of this screening criterion, they harvested 452 radial arteries and experienced no instances of vascular compromise in these patients. Five percent of patients tested were not suitable for RA harvesting using this method. While these three reports support the use of the Allen test as a screening device, the results of these studies cannot be generalized as they assessed the Allen test without comparing it to an objective technique. There have been few comparative studies investigating the relative efficacy of the Allen test.

In 1981, Husum and Berthelsen compared the modified Allen test with thumb systolic arterial pressure as measured by strain-gauge plethysmography in 118 patients. A normal Allen test recovery time was defined as less than six seconds while an abnormal result with plethysmography was defined by a thumb systolic pressure of less than 40 mm Hg after RA occlusion. Using these criteria, they obtained unusually high results. For example, they found that the predictive value of a negative Allen test was 0.99, that is, in only 0.8% of cases did the Allen test falsely indicate the adequacy of the collateral hand circulation. At the same time, however, they also found that the Allen test had a very high false positive rate. It falsely indicated an inadequate collateral circulation in 50% of positive tests.

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In 1999, Starnes and colleagues published the results of a study in which 129 consecutive patients, referred for preoperative evaluation of hand circulation before coronary artery bypass grafting, were assessed by using both the modified Allen test and photoplethysmography.\textsuperscript{292} The modified Allen test was performed using a Doppler probe to assess blood flow in the superficial palmar arch. A decrease in the audible Doppler signal with RA compression was considered a positive modified Allen test. The digital artery systolic pressure was measured in both the thumb and index fingers. In this study, an abnormal result was defined as a reduction in digital artery systolic pressure with RA compression of equal to or greater than 40 mmHg. Using this criterion, they found that 50 percent of extremities with an abnormal modified Allen test had a digital blood pressure reduction of less than 40 mm Hg indicating a high false positive rate. In terms of false negatives, 9 percent of cases with a negative Allen test experienced a reduction in blood pressure of 40 mm Hg or more. However, the validity of this study’s findings is questionable given the flawed nature of the criterion used to identify abnormal circulation. For example, in patients who have low digital artery systolic pressure before RA compression, after RA compression the pressure can decrease to critical levels while producing a pressure reduction of less than 40 mmHg. In order to avoid this problem in our study we used the digital-brachial index, that is, the digital systolic blood pressure compared with the patient’s normal proximal systemic pressure.

There have been several reports showing a correlation between abnormal digital-systemic blood pressure indices and the risk of clinical ischemia.\textsuperscript{293} However, these studies examined the lower, rather than upper extremities. Thus, the cut-off of 0.75 used in our study to distinguish normal from abnormal digital


brachial indices, was derived from a study of peripheral vascular disease in the lower limb and we assumed that the optimal pressure for supplying the tissue in the upper extremity is the same as the lower extremity. According to the ankle-brachial index, the following indices are consistent with the following clinical diagnoses: normal (1.0 to 1.2), claudicating (0.5 to 0.9), existing tissue loss unlikely to heal (<0.5), irreversible ischemia (0.0), and non-compressible vessels secondary to medial calcification (>1.3).

Dumanian and colleagues recommend not using the RA when digital brachial indices are less than 0.75 or when there is a low pulse-volume recording ratio (<0.4) in the index finger with RA compression at the wrist. This was based on a previous study performed to evaluate lower extremity peripheral vascular disease. Using this method, the authors determined that 98 patients out of 122 (80%) were suitable for harvesting the RA.

In our study, when a TBIO ≥ 0.75 was defined as normal, the false negative rate was 21% of cases which passed the modified Allen test while being deemed as unsatisfactory according to the TBIO test. This means that among cases where we might decide to use the RA based on the normal modified Allen test alone, 21% would be potentially at risk from hand ischemia. In order to reduce the false negative rate, we recommend to reduce the threshold of the modified Allen test to 8 seconds based on TBIO. Of course, the presence of an abnormal TBIO does not necessarily translate into clinical ischemia as both the modified Allen test and thumb-brachial indices measure the events immediately after occlusion of the RA and do not take into account the subsequent compensatory events that lead to the development of the collateral circulation. On the basis of these results, we recommend using the TBIO only when the modified Allen test is abnormal, thus saving the time and cost of the TBIO test.

It must be noted at this point that our study suffers from two potential deficiencies. Firstly, the TBIO cannot necessarily be regarded as the gold standard of circulatory screening and therefore may not represent the most accurate baseline against which to measure the Allen test. Secondly, given that the data we used came from patients with coronary heart disease referred to the Cardiac Surgery Unit, questions might be raised about whether the results of this study are applicable to patients in other clinical settings.

This study sought to comprehensively assess the validity of the Allen test against an objective measurement of thumb systolic blood pressure. In our experience, because it is easy to perform, the modified Allen test is excellent for use as a screening test. In contrast, the TBIO is relatively time consuming and hard to measure. While the Allen test correlates reasonably well with the TBIO it has a high false positive rate. Therefore, we recommend the use of the modified Allen test for primary screening. In the event of an abnormal result, however, we suggest that a more sophisticated test, such as digital blood pressure plethysmography or Doppler ultrasound, be performed.

CONCLUSIONS

In conclusion, both the modified Allen test and the thumb-brachial indices can be used to determine the safety of RA intervention. Both methods, however, have certain pitfalls and should be performed and interpreted carefully. Our study found that when the modified Allen test was equal to or less than 10 seconds, it was safe to harvest the RA. If the modified Allen test was more than 10 seconds, there was still a possibility that the RA might be harvested. In these latter cases, we recommend the performance of an additional more accurate test, such as photoplethysmography, to evaluate the hand circulation.

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SUMMARY

In this chapter, I presented a study that examined and confirmed the efficacy and validity of the modified Allen test as a screening test for assessing hand collateral circulation by comparing it with the digital systolic blood pressure as measured by plethysmography. Based on sensitivity, specificity and false negative rates, this study identified the best cut off point for modified Allen test recovery time to be 8 seconds.

Comparing the digital systolic blood pressure as measured by plethysmography with the Doppler dynamic test (Chapter 6) for assessing the hand collateral circulation, I would recommend the use of the Doppler dynamic test instead of plethysmography in case of an abnormal modified Allen test for several reasons. Firstly, it is relatively simple. Secondly, it examines the anatomy and flow in the digital arteries simultaneously. Thirdly, as I describe in Chapter 5, ultrasound can also identify arterial intimal plaque, calcification and hypoplasia of RA and ulnar artery.
Chapter 8

Survival after Coronary Artery Bypass Grafting: Comparison of the Internal Thoracic Artery, Radial Artery and Saphenous Vein as the Second Graft of Choice

Introduction

Patients and Methods

Patient Population
Surgical Techniques
  Left and right internal thoracic arteries harvesting
  Radial artery harvesting
  Great saphenous vein harvesting
  Cardiopulmonary bypass and coronary anastomotic technique
Follow-up
Statistical Analysis

Results

Kaplan-Meier Estimated Survival
Cox’s Proportional Hazards Model

Discussion

Summary
Introduction

In this chapter I tested the hypothesis that the radial artery (RA) is a viable coronary artery bypass graft by undertaking a survival analysis. This analysis involved an observational study of a large group of patients who had received RA grafts for coronary artery bypass grafting (CABG). We modeled the survival data on patients who had had CABG with two conduits. The first graft used was the left internal thoracic artery (LITA) while the second graft used was the right internal thoracic artery (RITA), RA or saphenous vein (SV).

The aims of this study were to: (1) determine the survival rate of patients after CABG with RA, and (2) compare the mid-term survival data of the RA as a second graft compared with the SV and RITA while adjusting for the different risk factors for mortality after CABG.

Patients and Methods

Patient Population

Between 3 January 1995 and 26 June 2000, 1,231 patients who underwent isolated primary CABG at the Austin & Repatriation Medical Centre and Epworth Hospital using exactly two conduits were included in this study. Patients undergoing reoperative CABG, associated cardiac valvular repair/replacement, repair/resection of left ventricular aneurysm or other cardiac/vascular operations were excluded. The mean age of patients was 64.3 years with a standard deviation (SD) of 10.35 years. The data were prospectively collected, verified and entered into a database and maintained by Dr. John Fuller, Cardiologist, at the Epworth Hospital, Melbourne, Australia. The data definitions were compiled using the Society of Thoracic Surgeons’ definitions. The RA began to be used as a second graft at our Centre in 1995 and patients were recruited from this time onwards. Nineteen surgeons participated in this study. Graft selection for the second graft occurred at the discretion of the attending surgeons. We avoided using the RITA in older or diabetic patients. The collateral circulation of the hand was assessed before RA harvesting using the modified Allen test. A recovery time (the time
required for the color to return to the hand after release of the ulnar artery) of more than 10 seconds was regarded as a contraindication for RA harvesting. During surgery, grafts with obvious calcification were also excluded. Saphenous veins with varicosities were not used for grafting.

All patients received a left internal thoracic artery (LITA) as their first graft. The second graft used was the RA in 700 patients (56.9% of cases), the RITA in 333 patients (27.1% of cases), and the SV in 198 patients (16.1% of cases). Fourteen potential risk factors for death are summarized in Table 8.1.
### Table 8.1. Baseline clinical characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n=1,231)</th>
<th>RITA (n=333)</th>
<th>RA (n=700)</th>
<th>SV (n=198)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD) yrs</td>
<td>64.3±10.35</td>
<td>59.2±9.75</td>
<td>65.7±10.09</td>
<td>67.9±9.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex: male</td>
<td>75.9%</td>
<td>83.8%</td>
<td>73.9%</td>
<td>69.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20.1%</td>
<td>6.3%</td>
<td>23.4%</td>
<td>31.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>46.1%</td>
<td>36.6%</td>
<td>48.6%</td>
<td>53%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>6.1%</td>
<td>5.1%</td>
<td>6.6%</td>
<td>6.1%</td>
<td>0.7</td>
</tr>
<tr>
<td>Carotid disease</td>
<td>11.5%</td>
<td>6.6%</td>
<td>12.9%</td>
<td>15.2%</td>
<td>0.003</td>
</tr>
<tr>
<td>Cigarette smoker</td>
<td>54.4%</td>
<td>54.1%</td>
<td>53.3%</td>
<td>59.1%</td>
<td>0.3</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>2.6%</td>
<td>1.8%</td>
<td>2.9%</td>
<td>3%</td>
<td>0.6</td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td>3.7%</td>
<td>2.7%</td>
<td>3.9%</td>
<td>5.1%</td>
<td>0.4</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>5.9%</td>
<td>3.3%</td>
<td>7.4%</td>
<td>5.1%</td>
<td>0.03</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>38.5%</td>
<td>31.2%</td>
<td>38%</td>
<td>52.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urgent and emergency surgery</td>
<td>15.8%</td>
<td>15%</td>
<td>14.4%</td>
<td>21.7%</td>
<td>0.04</td>
</tr>
<tr>
<td>Ventricular function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>EF ≥ 50%</td>
<td>81.6%</td>
<td>85.6%</td>
<td>81.1%</td>
<td>76.8%</td>
<td></td>
</tr>
<tr>
<td>EF = 30-49%</td>
<td>16.5%</td>
<td>13.5%</td>
<td>16.9%</td>
<td>20.2%</td>
<td></td>
</tr>
<tr>
<td>EF &lt; 30%</td>
<td>1.9%</td>
<td>0.9%</td>
<td>2.0%</td>
<td>3.0%</td>
<td></td>
</tr>
<tr>
<td>No. of anastomoses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>66%</td>
<td>77.8%</td>
<td>56.7%</td>
<td>78.8%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>27.4%</td>
<td>21.6%</td>
<td>32.6%</td>
<td>18.7%</td>
<td></td>
</tr>
<tr>
<td>4-5</td>
<td>6.7%</td>
<td>0.6%</td>
<td>10.7%</td>
<td>2.5%</td>
<td></td>
</tr>
</tbody>
</table>

*P value for comparison of differences between the RITA, RA and SV groups.

**Surgical techniques**
Left and right internal thoracic arteries harvesting

Following a conventional sternotomy, the LITA, and then the RITA, were harvested with a pedicle containing the pleura, the transversus thoracis muscle and fascia, and the internal thoracic veins (Fig. 8.1). The dissection commenced at the lower end of the sternum, near the internal thoracic artery bifurcation, and extended proximally to the inferior border of the subclavian vein. On the right side, the internal thoracic vein was mobilized to its termination with the right brachiocephalic vein. The upper branches of the ITA, including the pericardiacophrenic artery, were ligated with small clips adjacent to the ITA. The pedicle was sprayed with 1 mmol of a solution containing 80mg/ml papaverine and Ringer’s lactate solution. Following the transsection of either the lower end of the RITA pedicle or its terminal branches, and prior to implantation, the free flow was checked to exclude any proximal obstruction. Two to three cc of an equal mixture of the papaverine and Ringer’s lactate solution mixed with blood (1mmol/l, pH 7.4) was injected into the distal end of the ITA or one of its terminal branches. The distal end was then clipped using hemostatic clips (Weck hemoclip, North Carolina, U.S.A.) and allowed to distend under arterial pressure.

Figure 8.1 The left internal thoracic artery (LITA), In situ, pedicle. The LITA can be seen emerging from the left chest through the pericardial window, lying on the heart.

Prior to the commencement of cardiopulmonary bypass, the right pedicle
Survival after radial artery grafting was passed through a window in the right pleura and pericardium, immediately anterior to the phrenic nerve, and its length assessed in relation to the left or right coronary artery system. If deemed inadequate, the right internal thoracic vein was divided by double clipping, using medium Weck hemoclips. The RITA was then similarly clipped at the level of the inferior border of the right subclavian vein. The graft was stored in the mixture of papaverine, Ringer’s lactate and heparinized blood.

**Radial artery harvesting**

The RA often was harvested concurrently with the LITA harvesting and sometimes before the sternotomy. The arm was supinated and abducted to 70 degrees from the torso, on the arm board. The incision was made from 2 cm below the elbow to 2 cm above the wrist, slightly medial to the line of the RA in order to avoid injury to the medial and lateral cutaneous nerves of forearm as described in Chapter 2. The distal third of the RA was superficial and covered only by the subcutaneous tissue. The proximal two thirds of the RA was covered by the brachioradialis muscle (Fig. 8.2a). The medial border of the brachioradialis muscle was divided and retracted laterally (Fig. 8.2b). This step can start at the distal or the proximal forearm. For the distal forearm the fascia lining above the RA was divided, then the dissection was continued proximally. It was necessary to divide the 3-4 branches from the RA which supply the brachioradialis superficially (Fig. 8.2c).

After the RA was fully exposed, it was mobilized with its two venae comitantes (Fig. 8.2d). Direct handling of the artery was avoided to prevent arterial spasm. Muscular branches were divided with metal clips, not too close to the artery to avoid compromising the lumen. The distal end of RA was double clipped and divided at about 2 cm above the wrist joint. Two to three cc of the same papaverine mixture used for the ITA was injected into the distal end of the RA (Fig. 8.2 e and f). Dissection was undertaken towards the bifurcation of the brachial artery proximally while the artery was dilated under arterial pressure. However injury to the venous plexus around the bifurcation was avoided to prevent arm edema. The recurrent radial artery, sometimes present, could be
divided. The proximal end of RA was double clipped and divided 1 cm below the brachial bifurcation. The RA was then stored in the papaverine and Ringer’s lactate solution until implantation.

Figure 8.2  The radial artery (RA) harvesting technique (Left forearm)
(a). The skin incision is made along an imaginary line from the centre of the bent elbow, three cm below the elbow, to the fore part of the styloid process of the radius, three cm above the radial styloid.
(b),(c). The radial artery is exposed.
(d). Complete mobilization of the radial artery,
(e),(f). The radial artery is dilated with the papaverine mixture under physiologic pressure.
Great saphenous vein harvesting

The SV was always harvested simultaneously with the ITA. Most of the SV used in this study was from the lower part of the leg. The patient was in the frog leg position. The incision was made just lateral to the anterior edge of the medial malleolus and followed the course of the vein. The tributaries of the vein were divided with silk no. 3-0 or metal clips using atraumatic techniques, holding the adventitia of the vein and avoiding excessive direct grasping of the vein wall. The distal end of the vein was double clipped divided at about 2-4 cm above the medial malleolus. The same papaverine and Ringer’s lactate solution mixed with blood (1mmol/l, pH 7.4) used to dilate the ITA and RA, was injected into the distal end of the SV, avoiding excessive pressure. The SV was then checked for the residual tributaries and divided. The proximal end was double clipped and the graft stored in the same solution as for the free RITA and RA.

Cardiopulmonary bypass and coronary anastomotic technique

Cardiopulmonary bypass was performed at 34°C and combined antegrade and retrograde blood cardioplegia at 25°C employed, using a single cross clamp for all distal and proximal anastomoses. All distal anastomoses were performed using 7/0 polypropylene sutures with the pedicle attached to the adjacent epicardium. Sequential anastomoses were performed when the grafts and target arteries were suitable. Proximal anastomoses, if required, were performed directly with the ascending thoracic aorta using a continuous 6/0 polypropylene suture. Postoperatively, the mean arterial pressure was maintained at 70 to 80 mmHg or above, with a cardiac index of over two l.min⁻¹.m⁻² and a systemic vascular resistance of greater than 800 to 1,000 dynes.sec.cm⁻⁵. Dilatation of the arterial grafts relied on topical papaverine and the systemic vasodilators nitroglycerine, sodium nitroprusside, or the phosphodiesterase III inhibitor (milrinone) were added to produce a cardiac index of three l.min⁻¹.m⁻².

Follow-up

Patients were followed up by mailing questionnaires and by contacting general practitioners and surgeons. Deaths were confirmed by reference to the
Survival after radial artery grafting

Australian National Death Index, a computer-based system that updates its records on a 3 monthly basis, and used by the Australian Institute of Health and Welfare to track all deaths. The average follow-up time in our study was 32.9 months (SD 18.8). The primary end point of this study was all-cause mortality.

Statistical Analysis

Continuous data are presented as means and standard deviations (SD). Differences in baseline characteristics were compared between patients in the three different second graft groups by analyses of variance and chi-square tests. The Kaplan-Meier method was used for the unadjusted survival of the patients in the graft groups separately. The logrank test was used to test the difference in survival rates.

To control for potential imbalances in baseline risk factor variables related to the non-randomized nature of this study, we used Cox’s proportional hazards model to adjust for the type of second graft used, the individual surgeons involved, and the 14 other potential risk factors shown in Table 8.1. The variables included in the model were all those considered prior to surgery to be major risk factors for survival following CABG as well as any other statistically


significant differences between the second graft groups. The variables considered to be prior major risk factors were: age, gender, diabetes, hypertension, peripheral vascular disease, carotid disease, positive history of cigarette smoking, associated valvular lesion, previous myocardial infarction, urgency of operation, ventricular function, number of anastomoses, type of second graft, and surgeons. The surgeon involved was included in the model because of different graft preferences, surgical abilities and techniques. Ten surgeons who each performed fewer than 22 operations over the whole study were combined into one group. Two other variables which might be considered as important risk factors in general are congestive heart failure and renal failure. However, for patients eligible for this study CHF and renal failure are quite rare: there were six subjects with CHF among the 1,231 patients analysed, and none of these died. There were 10 patients with renal failure, one of whom died; this patient had a saphenous vein graft. The Grambsch-Therneau test of goodness-of-fit for Cox’s proportional hazards model was used to validate the model.\textsuperscript{299} A $P$-value of less than 0.05 was assumed for statistical significance. All analyses were done using the SPSS version 10.0 (SPSS Inc. Chicago, Illinois, USA) and S-Plus 4 statistical package (MathSoft, Seattle, Washington, USA).

**RESULTS**

Of 1,231 patients, age, gender, diabetes, hypertension, carotid disease, presence of mitral regurgitation, previous myocardial infarction, urgent/emergency surgery, and a number of anastomoses showed statistically significant differences among the three graft groups (Table 8.1). There was also a significant difference in graft selection and distribution between surgeons ($P < 0.001$). Two thousand nine hundred and seventy-four coronary artery anastomoses were performed. The LITA was used as an \textit{in situ} graft in 98\% (1418/1447) of anastomoses. The RITA was used as an \textit{in situ} graft in 24.4\%.

Survival after radial artery grafting

(86/352) of anastomoses. Sequential anastomoses were performed in the LITA, RITA, RA and SV in 216 (14.9%), 19 (5.4%), 253 (26.5%) and 24 cases (10.8%), respectively. There was no statistically significant difference in terms of target coronary artery (left versus right coronary artery) or degree of stenosis of grafted coronary artery (low versus high grade stenosis) in the three graft groups (Table 8.2).

Forty-one patients died during follow-up (4/333 in the RITA group, 20/700 in the RA group and 17/198 in the SV group). The median time of death was 8.1 months and ranged between 0.01-34.8 months. Fifteen (36.6%) were operative deaths (< 30 days after operation) and 26 (63.4%) were late deaths (≥30 days after operation).

Table 8.2. Comparison of target coronary artery and coronary artery stenosis between the right internal thoracic artery (RITA), the radial artery (RA) and the saphenous vein (SV) groups.

<table>
<thead>
<tr>
<th>Type of second graft</th>
<th>Type of coronary artery</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RITA</td>
<td>RA</td>
</tr>
<tr>
<td>Target coronary artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>200 (56.8%)</td>
<td>570 (59.8%)</td>
</tr>
<tr>
<td>Right</td>
<td>152 (43.2%)</td>
<td>383 (40.2%)</td>
</tr>
<tr>
<td>Coronary artery stenosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (&lt;60%)</td>
<td>53 (15.1%)</td>
<td>121 (12.7%)</td>
</tr>
<tr>
<td>High (≥60%)</td>
<td>299 (84.9%)</td>
<td>832 (87.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>352</td>
<td>953</td>
</tr>
</tbody>
</table>

Kaplan-Meier Estimate

The observed survival rate at two years for the RITA group was 99.0% (95%CI, 97.9% - 100%). For the RA group, the survival rate at two years was 97.1% (95% CI, 95.8% - 98.4%) and for the SV group the survival at two years was 92.1% (95% CI, 88.4% - 96.0%). There was a statistically significant difference between these survival rates (P= 0.001, logrank test). At the three-years
follow-up, the number of subjects not censored had fallen to below 50% in the SV group, and the latest death in all three graft groups was between two and three years, therefore two years was chosen as the longest estimated survival time. However, the crude comparison of survival between the second graft groups is potentially biased because there were differences between the patient characteristics of each group. Figure 8.3 shows survival curves by type of second graft before adjustment for baseline differences. Observed and adjusted survival estimates by type of second graft over time are summarized in Table 8.3.

Table 8.3. Comparison of survival rate between the RITA, RA and SV groups.

<table>
<thead>
<tr>
<th>Time elapsed since surgery</th>
<th>RITA (n=333)</th>
<th>RA (n=700)</th>
<th>SV (n=198)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30d</td>
<td>327</td>
<td>0.994</td>
<td>0.997</td>
</tr>
<tr>
<td>1 yr</td>
<td>281</td>
<td>0.994</td>
<td>0.997</td>
</tr>
<tr>
<td>2 yrs</td>
<td>231</td>
<td>0.990</td>
<td>0.996</td>
</tr>
</tbody>
</table>

N = number at risk, Obs. = Observed, Adj. = Adjusted

Figure 8.3  Observed Kaplan-Meier Survival estimates with right internal thoracic artery (RITA), radial artery (RA) and saphenous vein (SV) as a second graft
Cox’s Proportional Hazards Model

The five explanatory variables that were statistically significant in the Cox’s model were age, urgent/emergency surgery, ventricular function, concomitant aortic stenosis, and type of second graft. The adjusted rate ratios and 95% confidence intervals (CI) of the variables included in the model are shown in Table 8.4.

In relation to the type of second graft employed, after statistically adjusting for the other 15 risk factors, the rate ratios were as follows: RITA versus RA: 0.55 (95% CI: 0.17 – 1.77, \( P = 0.3 \)); SV versus RA: 2.21 (95% CI: 1.05 – 4.65, \( P = 0.04 \)); SV versus RITA: 4.01 (95% CI: 1.21 - 13.3, \( P = 0.02 \)). The Grambsch-Therneau test of goodness-of-fit for Cox’s proportional hazards model was not significant (\( P > 0.9 \)), indicating that the data were consistent with the assumption of proportional hazards. Figure 8.4 shows survival curves by type of second graft after adjustment for baseline differences. The survival rate was significantly better in the patient group receiving the RITA and RA than the SV.
Figure 8.4  Kaplan-Meier survival estimates with right internal thoracic artery (RITA), radial artery (RA) and saphenous vein (SV) as a second graft, adjusted for the 15 other potential explanatory variables shown in Table 8.4.
Table 8.4. Results of Cox’s proportional hazards model: risk factors for death.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Reference</th>
<th>Index</th>
<th>RR* (95% CI)</th>
<th>P value</th>
<th>Overall P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>X yrs</td>
<td>X + 10 yrs</td>
<td>1.58 (1.05-2.39)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Urgent/ emergency</td>
<td>Elective</td>
<td>Urgent/ Emergency</td>
<td>2.81 (1.35-5.82)</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Ventricular function</td>
<td>EF ≥ 50%</td>
<td>EF=30-49%</td>
<td>1.97 (0.89-4.33)</td>
<td>0.09</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>EF &lt; 30%</td>
<td>5.93 (1.77-19.99)</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>Presence</td>
<td>Absence</td>
<td>4.79 (1.51-15.21)</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Type of second graft</td>
<td>RA</td>
<td>RITA</td>
<td>0.55 (0.17-1.77)</td>
<td>0.3</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>SV</td>
<td>2.21 (1.05-4.65)</td>
<td>0.036</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
<td>0.54 (0.27-1.08)</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes</td>
<td>No</td>
<td>0.93 (0.44-1.99)</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>Yes</td>
<td>No</td>
<td>1.85 (0.67-5.11)</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Carotid artery disease</td>
<td>Yes</td>
<td>No</td>
<td>1.11 (0.47-2.59)</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Yes</td>
<td>No</td>
<td>1.32 (0.63-2.75)</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>No</td>
<td>1.17 (0.60-2.27)</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoker</td>
<td>Yes</td>
<td>No</td>
<td>1.18 (0.59-2.36)</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td>Presence</td>
<td>Absence</td>
<td>1.40 (0.44-4.49)</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>Presence</td>
<td>Absence</td>
<td>0.88 (0.31-2.50)</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>No. of anastomoses</td>
<td>2</td>
<td>3</td>
<td>1.08 (0.49-2.40)</td>
<td>0.9</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 and 5</td>
<td>1.66 (0.53-5.20)</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Surgeon</td>
<td></td>
<td>Comparisons between individual surgeons not shown</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*RR (rate ratio) and 95%CI (confidence interval) for index category relative to reference category.
For risk factors at more than two levels, the overall P-value assesses the presence of any effect, while pairwise P-values are also shown.
DISCUSSION

This study identified the choice of second graft as a risk factor for death in addition to age, urgency of operation, ventricular function, and presence of aortic stenosis, after adjustment for other factors. Use of the SV significantly increased the rate of death - 2.21 compared with the RA and 4.01 compared with the RITA. The RITA demonstrated a non-significant reduction in mortality compared with the RA.

The study population was restricted solely to CABG patients receiving two conduits so that we could accurately assess the survival impact of the second graft. For the first time, we used the newly developed Australian National Death index from the Australian Institute of Health and Welfare, which enabled us to confirm accurately the patients’ status. This is similar to the linkage between valve surgery and the national death registry employed in the United Kingdom.300

We used appropriate statistical controls and adjusted for all recognized confounding factors. The rate of urgent or emergency surgery reflected the degree and severity of coronary artery disease such as acute coronary syndrome or left main artery disease. The number of anastomoses also reflected the extent of coronary artery disease and the actual number of arteries grafted. This also took into account the number of sequential anastomoses. We also adjusted for the surgeon performing the operation as this variable was associated with potential bias in terms of graft selection, myocardial protection and grafting technique. The coronary artery targeted and the degree of coronary artery stenosis, both factors considered to affect the clinical outcome and graft patency,301 were similar in the

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three graft groups. We were unable to adjust for a number of variables that may potentially affect the outcome of CABG, such as liver disease and other systemic diseases.

The RITA has a graft patency equivalent to that of the LITA when used as a pedicled graft. Furthermore, in several studies, the RITA has shown a survival benefit when used in addition to the LITA. However there are risks involved in using the RITA in elderly or diabetic patients. Therefore the RA has an important role to play in achieving complete arterial revascularization in patients with multivessel disease.

In 1998, Borger and colleagues demonstrated a significant decrease in sternal wound infections and blood transfusions in patients who received the RA as a second graft compared with the RITA. They also found no difference in the perioperative or intermediate term morbidity and mortality rate. In 2001, Cohen and associates reported the findings of a case-matched study in which grafting with the RA was compared to the SV. They found that the RA was associated with a lower early mortality and morbidity rate despite a high incidence of diabetes, hypertension and peripheral vascular disease in the RA group.


A drawback of this survival study is the lack of collaborative graft patency data. A number of re-angiograms have been performed for symptoms suggesting ischemia. However these are likely to produce a biased result. To address the issue of graft patency, we are conducting a prospective randomized controlled study, now in its fourth year, comparing the late graft patency in patients who receive a RITA, RA or SV as their second graft. Four hundred patients have been enrolled to date. The results are not available at present.

Our study suggests that using the RA in CABG is safe. The risk adjusted mortality rate of the RA group was significantly lower compared with the SV group but not significantly different to the RITA group. Even though the number of deaths was small over the five-year study period, a positive survival trend favoring the RITA and RA compared with the SV was demonstrated. A longer follow-up is required to demonstrate a clear difference between these three different types of second graft.

SUMMARY

This study indicates that the RA is safe for use in coronary artery bypass grafting. Furthermore, the RA offers a significant survival benefit compared with the SV when used as a second graft. The next chapter analyzes some of the scheduled angiography with a view to comparing the graft patency between the RITA, RA and SV from a randomised trial which is being conducted at the Cardiac Surgery Department, Austin & Repatriation Medical Centre, The University of Melbourne.
Chapter 9
Semi-quantitative and Quantitative Coronary Angiography of the Radial Artery, Internal Thoracic Artery and Saphenous Vein in an Elective Cohort

(a) Preliminary angiographic results of Australian Radial Artery Study Trial

Introduction

Patients and Methods

Study Protocol
Patients
Clinical follow-up
Study endpoint
Angiographic protocol
   Semi-quantitative Analysis
   Quantitative Analysis
Reproducibility of semi-quantitative and quantitative Analysis
Statistical Methods

Results

Clinical outcome
Angiographic results
Reproducibility of semi-quantitative and quantitative Analyses
Factors influencing graft stenosis

Discussion

Conclusion

(b) Angiographic and Quantitative Analysis protocol

Appendix

Australian Radial Artery Study Protocol
(a) Preliminary angiographic results of Australian Radial Artery Study Trial

Introduction

In the observational study discussed in the previous chapter we demonstrated a survival benefit in patients receiving the radial artery (RA) or the right internal thoracic artery (RITA) compared with the saphenous vein (SV) over a three-year follow-up period. Although there was a survival benefit associated with using the RA graft in addition to the left internal thoracic artery (LITA), there was a concern that the benefit was not directly related to the RA. The most important information regarding the efficacy of the RA is the graft patency.

In this chapter I analyze the early results of a prospective randomized controlled trial, the Australian Radial Artery Trial. This trial is currently in progress at the Austin & Repatriation Medical Centre (1996 - ) examining the graft patency of the RA compared with that of the free RITA and SV.

Quantitative coronary angiography (QCA) is a well-established technique measuring the degree of stenosis in the coronary artery. However, there is little known about the QCA of grafts after coronary bypass grafting. In early angiographic follow-up of the graft, there is usually no or mild stenosis compared with the native coronary artery. Mild stenoses are measurable by QCA and should not affect the reliability. In general the wider the vessel, the more pixels across the vessel are available for analysis, the higher the reliability of QCA.

The aims of this study were: (1) to evaluate the reproducibility of semi-quantitative (SQCA), i.e. a planimetry measurement, and quantitative coronary angiography (QCA), a digital assessment, for analyses of diameter and area loss

of target arteries and grafts, respectively; (2) to evaluate the early diameter and cross-sectional area loss of the grafts using semi-quantitative and quantitative coronary angiography; (3) to compare the diameter and area loss of RA vs RITA and RA vs SV; (4) to determine factors influencing diameter and area loss in the grafts; and (5) to establish the QCA technique for graft evaluation.

PATIENTS AND METHODS

Study Protocol

Patients scheduled for primary coronary artery bypass surgery using more than one graft were included in this study. To be included, they were required to have at least two coronary artery stenoses of ≥ 70% and a coronary artery diameter ≥ 1.5 mm. They were randomised to receive a RITA, RA or SV as their second graft in addition to the left internal thoracic artery. Additional saphenous veins were used to complete the reconstruction when more than two grafts were necessary. This study consisted of two clinical trials randomized to: (1) RA versus RITA; and (2) RA versus SV based on age and presence or absence of diabetes.

Trial 1. (RA-RITA Trial)

RA versus free RITA in patients aged ≤ 70 years or diabetic patients ≤ 60 years.

Trial 2. (RA-SV Trial)

RA versus SV in patients aged >70 years or diabetic patients > 60 years.

Exclusion criteria

1. Renal disease with a creatinine > 0.30 mmol/L.
2. Chronic heart failure (NYHA Class III or IV or ejection fraction < 35% on angiography or radionuclide ventriculography).
3. Associated major illnesses e.g., malignancy.
4. Body mass index (BMI) > 35 weight (kg)/height² (m²).
5. Acute presentation, that is, those patients who had an acute myocardial infarct in the week leading up to surgery or who presented with cardiogenic shock.
6. Technical exclusions e.g. sequential grafting.
Specific exclusion criteria in RA-RITA Trial.

1. Inability to use the RA because of an abnormal Allen test (> 10 seconds).
2. Inability to use the free RITA due to, for example, previous chest trauma.
3. FEV\textsubscript{1} < 50% of expected value.

Specific exclusion criteria in RA-SV Trial.

4. Inability to use the RA because of an abnormal Allen test (> 10 seconds).
5. Inability to use the SV due to, for example, varicose veins or past trauma.

Randomization was carried out by the Statistical Consulting Centre, the University of Melbourne, using random number generation in the statistical package “Minitab”. Opaque envelopes containing randomly allocated numbers were provided in small batches to the Research Nurse responsible for record keeping and obtaining informed consent. Each envelope had the individual randomization sequence number printed on the outside of the envelope. Details of the subject to be randomly allocated and the date were recorded on the outside of the envelope prior to opening. The staff involved in the clinical management of the patients and in the surgical interventions had no involvement in the randomization procedure.

Intraoperative exclusion

RAs with extensive calcification were excluded from use. Damaged grafts were also excluded. Patients whose chosen graft conduit proved unsuitable intra-operatively were included in the analysis on an intention-to-treat basis.

Patients

Three hundred and ninety four patients undergoing surgery between June 1996 and December 2000 were enrolled in this study. Two hundred and fifty four patients were included in the RA-RITA Trial. These consisted of 128 and 126 patients who were randomized to the RA and RITA groups, respectively. One hundred and forty patients were included in the RA-SV Trial. Sixty-seven patients were randomized to receive a RA and 73 patients a SV. The graft harvesting and
operative techniques were the same as described in Chapter 8.

**Clinical follow-up**

All patients (including control patients) were given calcium channel blockers (amlodipine 2.5-5 mg daily) for six months after surgery on the unproven assumption that spasm in the muscular RA conduit would be less frequent. This was undertaken using the long acting dihydropyridimone, amlodipine 5 mg per day (reducing to 2.5 mg per day if hypotension occurred). Clinical follow-up by the research nurse was carried out every year by telephone or mail and by contacting the surgeons involved.

**Study endpoints**

The study endpoints were: (1) clinical outcomes including recurrent angina, recurrent myocardial infarction, re-operation, and death; and (2) graft patency. I have focused on the evaluation of semi-quantitative (SQCA) and quantitative analysis (QCA) for measuring the diameter and cross-sectional area loss of the target arteries and grafts, and early angiographic results in this chapter.

**Angiographic protocol**

The planned coronary angiographic schedule for postoperative catheterisation was organized as follows: 10% of patients during the first month, 10% at two years, 20% at five years, 30% at 7.5 years, and 30% at 10 years. Forty-two patients addressed in this chapter had re-angiograms over the first four years. All patients had further randomization to determine which one of the five times angiography was to be scheduled.

Diagnostic coronary angiography was performed using the standard femoral approach. Selective injections of the native coronary arteries and grafts were obtained. The native coronary arteries and grafts were examined in left oblique (LAO) and right oblique (RAO) projections. These were subjected to both semi-quantitative and automated quantitative analyses. An analysis was also made of the preoperative coronary angiograms of those vessels on which the study graft was subsequently placed (target coronary artery).
QCA of the study graft and native coronary artery was performed using the Quantitative Coronary Analysis, Cardiovascular Measurement Solutions system, Version 4.0 (QCA-CMS®, Leiden, The Netherlands). Since 1997, coronary arteriograms were acquired in digital format using the Toshiba X-Ray catheterization system; image data was exchanged on CD using the Digital Imaging and Communication standard (DICOM, Toshiba). Conventional 35 mm cinefilms were analyzed by semi-quantitative coronary angiography.

**Semi-quantitative analysis**

At re-angiography, the severity of stenosis was assessed in two planes (planimetry) by two different experienced observers and a cardiologist. Measurement was taken of the most severely diseased segments of the coronary artery and graft using a standard ruler. The severity of stenosis of the coronary artery and study grafts was recorded as “percent diameter stenosis”, which represented the percent reduction in diameter relative to nearby “normal” lumen.

Grafts in which the diameter was less than 1.0 mm and localized stenosis was not evident were regarded as indicating the “string sign”. The proximal and distal anastomoses of the graft and trunk were assessed separately.

**Quantitative analysis**

The following criteria were used to decide the most appropriate frame to be analyzed: (1) the graft/coronary artery segment should be well-filled with contrast medium; this is usually achieved by selecting an image from the diastolic phase in the second or third cardiac cycle following the contrast administration; (2) the stenosed segment of the graft/coronary artery should be clearly visible, preferably without any overlap from other vessels or side branches.

For each graft and coronary segment, a corresponding calibration factor was obtained on the basis of the size of the contrast catheter. The image selected for calibration was not necessarily the same image in which the obstruction was measured. Criteria for calibration and frame selection included: (1) the nontapering segment of the catheter being visible with a sufficient length (~ 2
cm), and (2) the catheter not being obscured by contrast flowing back into the aorta. As a result, the catheter image selected was usually in the early phase of the cardiac study.

The study grafts and native coronary arteries were measured using automated contour detection algorithms. The start and end points of the analyses for the native coronary artery were defined according to the bifurcations of major arterial segments as recommended by the American Heart Association. The start point for the study graft was defined as the normal part of the graft near the aorta and the end point was at the distal anastomosis. QCAs were performed on two projections: the most severe lesion and the perpendicular view where possible. The segment under consideration was positioned in the center of the field where distortion is minimal.

Lesions not measurable by QCA included those with stenosis > 85% that could not be reliably edge tracked or segments with diffuse disease or ectasia that had no reliable reference diameter. Lesions in the graft or coronary artery that were smaller than 1.0 mm could not be measured by QCA.

Automated detection of the arterial contours

Following calibration of the catheter size and definition of the start and end points of the analyzed segment, QCA-CMS software automatically created the pathline. The line lay entirely inside the selected vessel connecting the start and end point. The contour detection procedure was carried out automatically. The pathline and the vessel contour were adjusted with manual correction in particular areas by the analyst, in case of some unavoidable objects such as wires. An accurate centerline was computed. A diameter function was determined by


measuring the width of the vessel for every position along this centerline and subsequently the site of maximal percent diameter stenosis was defined. The reference diameter was defined as the estimated size of the vessel prior to the occurrence of a focal obstruction shown as a straight line in the diameter function. This reference diameter function was assessed by a linear regression technique, which was calculated through all points of the vessel diameter function (Figure 9.1).

**Figure 9.1** The diagram shows the true and reference diameter functions where the straight line is the interpolated reference diameter function (red line). The position of the minimum obstruction (o) and reference diameters (r) and the proximal (p) and distal (d) boundaries of the obstruction are indicated by the vertical lines.

Percent diameter and area stenosis were calculated from the following formulas. Circular cross sections have been assumed when calculating areas from diameter (Area = \(\pi \text{diameter}^2/4\)).

Diameter stenosis = \((1 - D_{obtr}/D_{ref}) \times 100\%\)

Area stenosis = \((1 - A_{obtr}/A_{ref}) \times 100\%\)

\(D_{obtr}\) = the obstruction diameter

\(D_{ref}\) = the reference diameter at the position of the obstruction

\(A_{obtr}\) = the obstruction area

\(A_{ref}\) = the reference area at the position of the obstruction
Reproducibility of Semi-quantitative and Quantitative analysis

To assess the intraobserver variability of the SQCA, 22 preoperative cinefilms containing a coronary artery stenosis of target artery were repeatedly analysed at two months interval. Coronary obstructions were analyzed in a standardized manner, i.e., from one major bifurcation to the next of the native coronary artery according to the recommendations of the American Heart Association.

For QCA, 22 different digital study graft coronary angiograms were used. Study grafts were analyzed in a standardized manner, i.e., from the proximal to the distal anastomoses of the graft. The same set of selected frame images were reanalyzed three days later by the same observer without knowledge of the first analysis session. This meant that the observer defined the beginning and end
points of grafts based on the proximal and distal anastomoses visible in the images, but without knowing the precise positions of these reference points from the corresponding analyses. To evaluate additional variations in terms of frame selection, reanalyses were also performed two months later without any knowledge of the first analysis except the identification of the grafted target artery.

The digitized target artery angiography (n=7) and the cinefilm of study grafts (n=13) were not used for the reliability study because of the small number of samples.

**Statistical methods**

All data were expressed as mean ± SD. Intraobserver variability was estimated by calculating the differences between paired measurements according to the method of Bland and Altman\textsuperscript{310}: Repeatability coefficient = (2.77 × estimated standard deviation of repeat observations on the same angiogram). This means that approximately 95% of differences between two repeated measurements would be less than the repeatability coefficient. The coefficient of variation (CV) of the two means was computed in order to compare the difference of the repeatability of SQCA and QCA, and between the interval differences of QCA. The CV was calculated as: CV = 100 (estimated standard deviation of repeat observations on the same angiogram)/ mean of the two measurements. Correlation coefficients were also used. As some of the data did not follow a bivariate normal distribution, the usual test of correlation based on Pearson’s sample correlation coefficient may not have been reliable. Therefore, the significance of correlations was tested using Spearman’s rho, a non-parametric test which does not assume bivariate normality.

The differences at baseline between the two groups in each trial were examined. Statistical tests were carried out: t-tests for continuous variables and Fisher’s exact test (2-sided) for binary variables.

Linear model, univariate analysis was used to estimate the mean differences in degrees of diameter and area stenosis in two different grafts (RA vs RITA or RA vs SV) adjusted for the time interval between the operation and the angiography.

Linear models were fitted to assess the effects of the following five factors on the postoperative diameter and area stenosis of the study grafts: age at operation, gender, time from operation to angiography, diabetes, smoking history, and types of study graft. This analysis was only performed for the RA-RITA trial, because of the small sample size in the RA-SV trial.

RESULTS

Demographic data are summarized in Table 9.1. In both trials, patients randomized to receive either RA, RITA or SV had similar clinical risk factors for vascular disease and number of vessels grafted. One patient in the RA-RITA trial, randomised to the RITA, did not have the RITA harvested and was therefore excluded from the angiographic analysis.

There was no significant difference in degree of target coronary artery stenosis (RA group: 71.21±24.11 vs RITA group: 66.36±19.64, P =0.6) in the RA-RITA trial and also in the RA-SV trial (RA group: 70.95±19.39 vs SV group: 75.43±17.83, P =0.6). Table 9.2 shows the native target coronary artery in each group.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RA-RITA Trial</th>
<th>RA-SV Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RA (n=12)</td>
<td>RITA (n=13)</td>
</tr>
<tr>
<td>Age (mean±SD) years</td>
<td>60.7±6.7</td>
<td>60.7±6.3</td>
</tr>
<tr>
<td>Sex: male</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Cigarette smoker</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>No. of anastomoses</td>
<td>2.85±0.80</td>
<td>3.0±0.71</td>
</tr>
<tr>
<td>Interval to angiography (days)</td>
<td>237.7±210.8</td>
<td>516.8±432.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Target artery</th>
<th>RA-RITA Trial</th>
<th>RA-SV Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RA (n=12)</td>
<td>RITA (n=13)</td>
</tr>
<tr>
<td>Diagonal</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Marginal</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Posterior descending from right coronary</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

Clinical outcome
All patients in the RA-RITA trial have survived. Two patients in the RA-SV trial died at 23 and 36 months after operation, respectively. Both of these patients received RA and both RAs were patent (one had no stenosis and the other had a 9.31% diameter stenosis in the RA) at the time of scheduled angiography. One case passed away at home in his sleep. An autopsy report indicated the cause of death as ischemic heart disease with generalised atherosclerosis, chronic obstructive airway disease as contributing factors. The other case had underlining chronic renal failure and died in nursing home, unknown cause of death.

**Angiographic results**

Of 42 angiograms, four patients had localized stenosis of the study graft at anastomotic sites. One RA in the RA-RITA demonstrated a “string sign” in the RA-RITA trial and was excluded from the semi-quantitative and quantitative analyses.

**Reproducibility of semi-quantitative and quantitative analyses**

**Semi-quantitative analysis**

Table 9.3 shows the intraobserver variation of the SQCA of the target coronary artery segments at two months interval. There was moderate correlation between the two measurements (rho = 0.67, \( P = 0.001 \)). The coefficient of variation is relatively high. Bland-Altman plots were performed to demonstrate the variability within observer (Figure 9.3).
Table 9.3  Test-retest reliability of semiquantitative (SQCA) measurement of the target coronary artery segment at 2 months interval.

<table>
<thead>
<tr>
<th></th>
<th>Mean±SD (%)</th>
<th>rho</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Mean diameter stenosis</td>
<td>72.94±16.98</td>
<td>0.671</td>
<td>0.001</td>
</tr>
<tr>
<td>2nd Mean diameter stenosis</td>
<td>73.23±18.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean difference*</td>
<td>-0.29±11.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeatability Coefficient†</td>
<td>22.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coefficient of variation†† (%)</td>
<td>31.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Mean difference between paired measurements (1st and 2nd measurements)

†Repeatability coefficient = \((2.77 \times \text{estimated standard deviation of repeat observations on the same angiogram}) = \) approximately 95% of differences between two repeated measurements will be less than the repeatability coefficient

††Coefficient of variation = \(100(\text{estimated standard deviation of repeat observations on the same angiogram)/ mean of the two observations}\)

Figure 9.3 Reproducibility of the diameter stenosis measured by semi-quantitative analysis at 2 months interval: Bland–Altman Plots showing the differences in measurement within observer against the mean value.
Quantitative analysis

Table 9.4 shows the reliability of the diameter and area stenosis measurements from the QCA. There was a substantial increase in repeatability coefficient between the repeated measurements at 3 days and the repeated measurements at the 2 months. Figures 9.4-9.7 plot the differences between the two measurements against the mean of two measurements.

**Table 9.4** Intraobserver variability in the repeated analysis quantitative analysis (QCA) of bypass graft stenosis

<table>
<thead>
<tr>
<th></th>
<th>Intra-observer variability at 3 days interval (n=22 pairs)</th>
<th>Intra-observer variability at 2 months interval (n=22 pairs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD (%)</td>
<td>Mean±SD (%)</td>
</tr>
<tr>
<td></td>
<td>rho</td>
<td>P</td>
</tr>
<tr>
<td>1st diameter stenosis</td>
<td>19.07±9.85</td>
<td>0.919</td>
</tr>
<tr>
<td>2nd diameter stenosis</td>
<td>17.30±8.19</td>
<td></td>
</tr>
<tr>
<td>Mean difference</td>
<td>1.77±2.96</td>
<td></td>
</tr>
<tr>
<td>Repeatability Coefficient</td>
<td>6.65</td>
<td></td>
</tr>
<tr>
<td>Coefficient of variation (%)</td>
<td>36.6</td>
<td></td>
</tr>
<tr>
<td>1st area stenosis</td>
<td>33.58±14.80</td>
<td>0.919</td>
</tr>
<tr>
<td>2nd area stenosis</td>
<td>30.96±12.99</td>
<td></td>
</tr>
<tr>
<td>Mean difference</td>
<td>2.6±2.96</td>
<td></td>
</tr>
<tr>
<td>Repeatability Coefficient</td>
<td>9.11</td>
<td></td>
</tr>
<tr>
<td>Coefficient of variation (%)</td>
<td>28.2</td>
<td></td>
</tr>
</tbody>
</table>
Figure 9.4 Reproducibility of the diameter stenosis (at 3 days interval). Bland–Altman Plots showing the differences in measurement within an observer against the mean value.

Figure 9.5 Reproducibility of the area stenosis (at 3 days interval). Bland–Altman Plots showing the differences in measurement within an observer against the mean value.
Figure 9.6 Reproducibility of the diameter stenosis (at 2 months interval). Bland–Altman Plots showing the differences in measurement within an observer against the mean value.

Figure 9.7 Reproducibility of the area stenosis (at 2 months interval) Bland–Altman Plots showing the differences in measurement within an observer against the mean value.
Combined results of semi-quantitative and quantitative analysis of diameter stenosis of study graft

The average graft stenosis was 13.6±19.9% for the RITA (n=13) and 15.7±11.5% for the RA (n=12) in the RA-RITA trial at average 382.80±360.94 days of follow up (range 6-1546 days).

The average graft stenosis was 2.8±4.8 % for the RA (n=9) and 12.9±9.4% for the SV (n=7) in the RA-SV trial at average 385±343.45 days of follow up (range 30-1042 days).

Quantitative Analysis

Table 9.5 and Figures 9.8-11 show the diameter stenosis and area stenosis in the study grafts in RA-RITA Trial. There was no significant difference of graft stenosis between the RA and RITA in RA-RITA Trial. There was also no difference in graft stenosis between RA and SV in RA-SV Trial (Table 9.6, Figure 9.12 and 9.13). The comparisons between RA and RITA, and RA and SV, were adjusted for differences in the time interval between operation and angiogram using a general linear model with types of study graft (RA or RITA) as a factor at two levels, and ‘interval from the operation to angiography’ as a covariate. Therefore, the estimates of the treatment comparisons are not equal to the simple differences between the two treatment means. The estimates and 95% confidence intervals for the treatment comparisons are given as (RA – RITA) and (RA – SV), and are adjusted for ‘interval from the operation to angiography’.

**Table 9.5** Comparison of diameter stenosis and area stenosis by quantitative analysis (QCA) between grafts in the RA-RITA Trial adjusted for the difference in interval after CABG (at average 382.80±360.94 days of follow up).

<table>
<thead>
<tr>
<th></th>
<th>RA (n=8)</th>
<th>RITA (n=7)</th>
<th>Mean difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter stenosis</td>
<td>18.40±9.55</td>
<td>14.62±2.62</td>
<td>4.31 (-4.80, 13.41)</td>
<td>0.3</td>
</tr>
<tr>
<td>Area stenosis</td>
<td>32.62±15.20</td>
<td>27.04±4.52</td>
<td>6.48 (-8.08, 21.04)</td>
<td>0.4</td>
</tr>
</tbody>
</table>
Figure 9.8  Histogram of the diameter stenosis by quantitative analysis (QCA) of RITA grafts in the RA-RITA Trial

Figure 9.9  Histogram of the area stenosis by quantitative analysis (QCA) of RITA grafts in the RA-RITA Trial
Figure 9.10  Histogram of the diameter stenosis by quantitative analysis (QCA) of RA grafts in the RA-RITA Trial

Figure 9.11  Histogram of the area stenosis by quantitative analysis (QCA) of RA grafts
in the RA-RITA Trial

**Table 9.6** Comparison of diameter stenosis and area stenosis by quantitative analysis (QCA) between grafts in the RA-SV trial adjusted for the difference in interval after CABG (at average 385\(\pm\)343.45 days of follow up).

<table>
<thead>
<tr>
<th></th>
<th>RA (n=2)</th>
<th>SV (n=5)</th>
<th>Mean difference (95% CI)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter stenosis</td>
<td>10.99(\pm)2.36</td>
<td>18.02(\pm)4.03</td>
<td>-8.33 (-19.01, 2.35)</td>
<td>0.09</td>
</tr>
<tr>
<td>Area stenosis</td>
<td>20.74(\pm)4.23</td>
<td>32.67(\pm)6.50</td>
<td>-14.02 (-31.41, 3.37)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Figure 9.12** Histogram of the diameter stenosis by quantitative analysis (QCA) of SV grafts in the RA-SV Trial
Factors influencing graft stenosis

Linear models were fitted to assess the effects of the following five factors on the postoperative diameter and area stenosis of the study graft: age at operation, gender, time from operation to angiography, diabetes, smoking history, and types of study graft. The only factor that affected the diameter and area stenosis in the study graft in the RA-RITA trial was diabetes ($P=0.044$ and 0.036, respectively).

DISCUSSION

This preliminary angiographic result of the Australian prospective
randomized trial demonstrated that the RA was an excellent conduit comparable to the RITA, using both semiquantitative and quantitative analysis techniques. Using automated edge-detection methodologies allowed precise quantitative analysis of the diameter and area of graft stenosis. At 12 months after implantation, the diameter and area stenoses of the RA and RITA did not significantly differ from each other. In other words, the contour of the RA and RITA were quite smooth. These stenotic indices tended to be lower in the RA when compared with the SV; however the number of grafts was too small to draw a meaningful conclusion. Although a number of SVs demonstrated some degree of irregularity and stenosis, the diameter of SVs was much larger than the RA. There was no clinical significance from the diameter and cross-sectional area loss in the first 12 months. The hemodynamic significance of a stenosis depends on both degree of stenosis, diameter of the vessel, pressure gradient across the stenosis and distal vascular resistance. 

The only independent factor influencing the diameter and area loss of the grafts (QCA measurement) in the RA-RITA Trial was diabetes. The combined results of the SQCA and QCA were not used for comparison of diameter and area stenosis between the grafts and risk factors analysis because of unequal numbers of grafts analysed by SQCA technique in each group of the study graft.

Graft stenoses found in the angiographic analyses were: (1) in the trunk of the graft; and (2) in the area around the proximal and distal anastomoses. In this study four anastomotic problems (4/42, 9.5%) were found. Possible causes were an inadequate anastomotic techniques or vascular healing process. This study was primarily directed at the properties of the coronary artery bypass grafts rather than the surgical techniques or complex changes of vascular healing mediated by

growth factors and smooth muscle cell proliferation at the site of the anastomoses. Therefore, in this study I focused on the luminal changes in the trunk of the graft.

The limitations of the visual assessment included inter- and intra-observer variability, poor correlation with postmortem measurements of coronary stenosis and poor correlation with physiologic measures of coronary lesions. In this study we utilised SQCA using visual assessment and planimetry. This technique has demonstrated reproducibility compared with the QCA. From the reproducibility study, SQCA demonstrated a standard deviation of the difference between two measurements of 12%.

QCA techniques have resulted in substantial success in reducing the variability of anatomic measurements and assessment of coronary artery stenoses.


There were however some variations when different QCA systems were used. The technique may also give variable results depending on frame selection, selection of the normal reference segment and methods of edge detection. Sirnes and colleagues found that precision (SD of signed errors) for percent diameter stenosis in the same angiography ranged from 4.2% to 5.8%. Herrington and colleagues studied day-to-day variations in patients, equipment or variability in selection of frames for analysis. Coronary angiograms were reviewed from 20 patients who underwent diagnostic angiography followed by percutaneous transluminal coronary angioplasty on average of 2.9 days later. The coefficient of variation for QCA, which measures the same lesions from separate angiograms ranged from 8.11% to 14.01%. Average diameter was the least variable and percent diameter stenosis the most variable. Day-to-day variations in the patient, procedure and equipment, accounted for an average of 30% of the total variability. Of the remaining variability, only 13.26% was due to frame selection.

Lesperance and colleagues reported the measurement reproducibility of 24 vein grafts in 24 patients who had symptom-directed control angiography. Focal narrowings expressed in percent stenosis varied from 5 to 80% (mean 20.8 ± 15.9%). They assessed the reproducibility of measurements obtained from two separate imagings of the graft in the same view but at least 20 minutes apart, near


the beginning and at the end of the angiographic procedure (simulating baseline and end-trial examinations). The SD for differences in measurements (variability) was 3.72% for the percent diameter stenosis.

In 2001 White and colleagues reported variability inherent in repeated studies of atherosclerotic saphenous vein grafts during the course of the Post Coronary Artery Bypass Graft (CABG) clinical trial, a randomised controlled trial designed to assess whether a strategy of lipid lowering (aggressive vs moderate) or low-dose warfarin anticoagulation could prevent atherosclerotic changes in saphenous vein grafts. In this study, they used the coefficient of variation (CV) as in our study and a new way of evaluating measurement error, “percent increase in standard deviation among patients”. The difference between these two methods is that the CV takes into account the mean of the observation but not in the “percent increase in standard deviation among patients”. For repeated angiographic views within a short time period, the variability of calculation of lesion minimal diameter increased by 1.5% in standard deviation among patients and CV was 5.32%, whereas the increase in standard deviation among patients after repeating the entire process of quantitative angiographic readings was 6.4% and CV 8%. The CV for the percent stenosis in this study was high compared with the “percent increase in standard deviation among patients”. For repeated angiographic views within a short time period, the variability of calculation of percent stenosis increased by 2.5% in standard deviation and CV 11.9%, whereas the increase in standard deviation among patients for repetition of the entire process of quantitative angiographic readings in the follow-up angiogram increased variability 21% and CV was 95.7%. In my opinion, the CV is more appropriate for evaluating the measurements error because it takes the mean of the magnitude of the dimension under inspection into account. A bigger magnitude of the dimension of observation will have a smaller CV, in other words when

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measuring a big magnitude of the dimension, a small measurement error perhaps is not important. However when measuring a small magnitude of the dimension, the small measurement error is important. The second point is that in White’s study the angiogram was not blinded to the previous angiogram. They evaluated the films simultaneously, therefore the selected frame and reference points were not taken into account when assessing variability, unlike our study.

In my study, I evaluated the variation of the QCA when used for measuring the graft diameter and area loss. I found the variations were high compared with other studies that evaluated discrete coronary artery stenosis. Possible explanations are: Firstly, in the early angiographic graft study, there was no obvious discrete lesion. The start and end points of the pathline were defined near the proximal and distal anastomoses. As a result, I used the nine-inch image intensifier mode in order to evaluate the whole length of the study graft. This results in loss of sensitivity by the software when detecting the lesions due to a significant increase in the size of the individual pixels. Initially, I attempted to divide the graft into three segments. There was however some difficulty such as end-on graft and finding a dividing point, unlike the coronary artery anatomy in which the start and end points can be defined at the point of branches as described by the American Heart Association. Difficulty in defining the start and end points was also a cause of variation in the analysis. Secondly, although the same frame was used for the second analysis, there was a variation between observers’ definitions of start and end points. Thirdly, the diameter and area losses were minimal and often these were not detected by visual techniques. Therefore, the second analysis may have utilised a different frame and a different projection selection by the observer. Following the first analysis, a second reanalysis (two months’ interval) was undertaken without any knowledge of the original information. This resulted in substantially more variation when compared with the first reanalysis (three days). Fourthly, the sample size in our study was small, 22 pairs; increasing the sample size is likely to reduce the variations. Finally, variations occurred in the postoperative graft study as a result of sternal wires and overlapping shadows from the native coronary artery making it necessary to correct manually the automatically defined vessel contours. QCA variation could
also be attributed to poor imaging techniques e.g. overexposure or insufficient image contrast in grafts.

A specific limitation of this study was that the early angiograms of patients were recorded on conventional 35 mm cinefilm, which meant quantitative analysis could not be performed at this time. Secondly, the earlier angiograms were not primarily set up for QCA, the catheter used was not large enough for accurate calibration. The most common catheter size used in this study was a 5 French catheter making calibration unreliable. Therefore, some significant values such as the stenotic flow reserve\textsuperscript{323}, lesion diameter, reference diameter could not be measured accurately and were omitted. In addition, some angiograms were recorded on VHS videotape and the quality was unacceptable for quantitative coronary angiography.\textsuperscript{324} I have now established a coronary angiography protocol with colleagues from the Leiden University Medical Center, The Netherlands as described in the next section.

**CONCLUSION**

Quantitative analysis of coronary artery grafts can be performed. The reproducibility can be increased by improving coronary angiographic techniques, defining rigid criteria of start and end points, and careful selection of the frame to be analysed.

The early graft patency of RA, RITA and SV were excellent at an average interval of one year from implantation. There was no difference in graft stenosis between RA and RITA in young age patients and also no difference in graft stenosis between RA and SV in older age group. An independent factor


\textsuperscript{324} Reiber, Koning, van der Zwet and Schiemanck. Catheterization & Cardiovascular Diagnosis 1996; 37:32-8.
influencing the diameter and area loss in the graft in the younger group was diabetes regardless of the type of the graft (RA or RITA used). The reproducibility of QCA when analysing the bypass grafts needs to be established, a larger number of study grafts and a longer follow-up are required to make a firm conclusion about the relative graft patency of the RA, RITA and SV.
(b) Angiographic and Quantitative Analysis Protocol

Following are the protocols for future angiography and QCA developed in conjunction with Professor Johan H.C. Reiber, Laboratory for Clinical and Experimental Image Processing (LKEB), Department of Radiology at the Leiden University Medical Center, The Netherlands, and the Interuniversity Cardiology Institute of the Netherlands (ICIN), Utrecht, The Netherlands.

Coronary Angiography

Diagnostic coronary angiography is performed by using the standard femoral approach with a premedication (diazepam, 5 mg PO). All vasoactive medications are discontinued one to two days before the study. The angiogram is performed using catheters (Cordis Europa, Roden, The Netherlands) of six French or larger. TIMI frame counting method is performed for the study graft and left internal thoracic artery as a control. During angiography, the native coronary arteries anastomosed to the study graft and left internal thoracic artery graft are also injected. LAO and RAO views of the grafts and native vessel are obtained using a 6 to 7 inch image intensifier mode to avoid overlapping of the sternal wires. Patients receive 0.5 mg nitroglycerine sublingually to control vasomotor tone and the same dose of nitroglycerine is repeated every 20 minutes during the procedure. The nonionic contrast agent iohexol (Omnipaque, 350 mg iodine per ml, Nycomed, Oslo, Norway) is used. Great care will be taken to record the gantry settings (rotations and cranio-caudal angulations, table height, and height of the image intensifier) as well as nitroglycerine administration on specially designed forms.

Quantitative analysis protocol

All QCA will be performed using the Quantitative Coronary Analysis, Cardiovascular Measurement Solutions system, Version 4.0 (QCA-CMS®,

Leiden, The Netherlands). A physician experienced in QCA, blinded to the clinical data, selects the frames for analysis. The following criteria are used to decide which appropriate frame should be analyzed: (1) the graft/coronary artery segment should be well-filled with a contrast medium; this is usually achieved by selecting an image from the second or third cardiac cycle following the contrast administration; (2) the stenosed segment of the graft/coronary artery should be clearly visible, preferably without any overlap from other vessels or side branches; (3) The vessel or graft segments are in the centre of the field; (4) the projection is perpendicular to the long axis of the vessel and appropriate collimation is applied.

For each study graft and coronary segment, a corresponding calibration factor is obtained on the basis of the contrast catheter size. The image selected for calibration may not necessarily be the same as the image in which the obstruction is measured. Criteria for calibration frame selection included: (1) the nontapering segment of the catheter being visible with a sufficient length (~2 cm), and (2) the catheter not being obscured by contrast flowing back into the aorta. As a result, the catheter image is usually selected in the early phase of the cardiac study.

The study grafts and native coronary arteries are measured using automated contour detection algorithms. The study graft will be divided into three segments, proximal third, middle third and distal third according to the length of the graft. The start point for the study graft is defined at the normal part of the graft in each segment. Anastomotic lesions will be analyzed separately. QCA will be performed on two projections: the most severe lesion and the perpendicular view if available. The segment under consideration will be positioned in the centre of the field, where distortion is minimal. The start and end points of the analyses for the native coronary artery will be defined according to the

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bifurcations of major arterial segments as recommended by the American Heart Association.

Lesions unsuitable for QCA will include those with stenosis > 85% that cannot be reliably edge tracked, and segments with diffuse or ectasis disease that do not have reliable reference diameter.

The mean, standard deviation, range of diameter and area of analyzed segment will be recorded, as will obstruction, reference, percent stenosis of diameter and area of the obstructed segment. The length of obstructed segments also will be recorded. Flow-related measurements (Poisseuille resistance, turbulent resistance) are computed from the geometry of the obstruction. This stenotic flow reserve is derived using the model of Kirkeeide and Gould. This model is based on fluid dynamic equations.

APPENDIX

AUSTRALIAN RADIAL ARTERY STUDY PROTOCOL

BACKGROUND

One of the major challenges facing medical practitioners today is the prevention and treatment of ischemic heart disease. The enormity of the problem is highlighted by the fact that half of all deaths in the developed world are caused by coronary artery disease [Mueller 1997]. Since the 1960s, a common method of treatment has been coronary artery bypass surgery. Not surprisingly, however, the techniques and types of bypass surgery performed have changed over the years. In particular, recently there has been a shift towards using arterial rather than venous conduits and treating patients with multivessel disease.

The first coronary artery bypass graft with a successful clinical outcome was performed in 1964 using the saphenous vein [Garrett 1973]. Despite reports of good results using the internal mammary artery as a bypass graft [Barner 1975; Geha 1975; Tector 1976], up until the 1980s the saphenous vein was the conduit of choice for coronary artery bypass grafting. In 1983, however, Campeau et al reported that the vein grafts examined had a patency rate of only 63% at 10 to 12 years [Campeau]. Meanwhile, a 1986 study reported better survival rates for patients who had received both internal mammary artery and saphenous vein grafts compared with those who were only given vein grafts [Loop].

The accumulated evidence from studies of long-term graft patency confirmed the superiority of internal mammary artery over saphenous vein grafts [Cameron 1996] and saw a resurgence of interest in arterial revascularisation. The shift towards multi-vessel grafting and the increasing number of reoperations [Grinda 1998] being performed led to a search for other arterial conduits that might be suitable for grafting, such as the RGEA [Pym 1987; Lytle 1989; Suma 1993] and the inferior epigastric artery [Puig 1990; Mills 1991; Buche 1992]. While these arteries (in particular the gastroepiploic artery) have demonstrated good early patency rates, morphologically they have some limitations.
The radial artery, first used for coronary artery bypass grafting by Carpentier and colleagues in 1973 [Carpentier 1973], is similar in length and size to the internal thoracic artery, has a similar diameter to the coronary artery and is easily harvested from one or both arms in most patients. It can be used as a single graft, anastomosed in a ‘Y’ fashion with the internal mammary artery, or used as a sequential graft. Furthermore, the radial artery can be used instead of the saphenous vein as a supplementary graft in complete arterial revascularisation thereby avoiding the hospital costs and clinical complications associated with an incision in the leg [Buxton 1996]. Despite these potential advantages, however, the radial artery has been under-utilised as a graft conduit due to the early publication of two reports indicating that the radial artery has a poor short to midterm patency rate [Curtis 1975; Fisk 1976]. In 1992, however, a study reinvestigating the viability of the radial artery as a graft conduit found that the patency rate of radial grafts was 93% at 9 months, better than the reported patency of free internal thoracic arteries (69%) [Acar]. Following this report, several cardiac centres in Europe and North America confirmed these results [Calafiore 1995, Brodman 1996]. The improvement in the results of radial artery grafting in the 1990s is thought to be due to better harvesting techniques and the use of calcium channel blockers to prevent vasospasm and early graft occlusion [Reyes 1995]. While the internal mammary artery remains the first choice of most surgeons, these improved results have seen the radial artery being increasingly used as an alternative to the saphenous vein [Buxton 1997a; He 2000]. However, while the improvement in the early results of radial artery grafting are encouraging further follow-up is required to establish the long-term patency and survival rates associated with using this vessel [Fremes 1995].

PATENCY DATA

Radial artery

There is mounting evidence supporting the excellent short-term patency of the radial artery as a coronary bypass graft [Chen 1996; Brodman 1996]. However, there is a relative lack of data concerning long term patency. Calafiore and colleagues’ 1995 study of 148 patients who underwent bypass grafting with a radial artery graft found that at follow-up angiography the early patency rate (30
days, 41 patients) was 100% while the late patency rate (mean 14 months, 30/32 patients) was 94% [Calafiore 1995]. A 1996 study found that in 61 patients who had angiography following radial artery grafting 97% were patent in the early post-operative period while in the 12 patients who had repeat angiograms at a mean interval of 9 months all grafts were patent [da Costa 1996]. In a longer term study of 68 patients with radial artery grafts, Possati and colleagues reported an angiographic patency rate of 92% 5 years after surgery [Possati 1998]. Acar and colleagues also conducted a five year follow up study, reporting a patency rate of 83% for patients receiving RA grafts and a rate of 91% for those receiving IMA grafts. They note that the difference between these two rates may be due to the different implantation sites of the two grafts with the RA mostly being grafted to the circumflex artery while the IMA was grafted primarily to the left anterior descending artery [Acar 1998].

**Internal mammary artery versus saphenous vein**

Comparative studies indicate that using either the internal mammary artery or the saphenous vein for coronary artery bypass grafting produces excellent short term results. For instance, both Goldman and colleagues and Sethi et al have reported a one-year patency rate of 93% for the internal mammary artery and 90% for the saphenous vein [Goldman 1990; Sethi 1991]. However, supporting the findings of Campeau and colleagues, a number of groups have demonstrated a marked gap between the long-term patency of saphenous vein compared with internal mammary artery grafts. Barner and colleagues, following up patients from 1 to 12 years after coronary artery bypa ss surgery, found the patency rate of the internal mammary artery versus the saphenous vein was 96% versus 94% at 1 year, 88% versus 74% at 5 years and 83% versus 41% at 10 years [Barner 1985]. In a 1988 study the cumulative 11-year patency rate was 88% for internal mammary artery grafts and 61% for saphenous vein grafts [Ivert 1988] while in a more recent study, the 10-year cumulative patency rate of internal mammary artery versus saphenous vein grafts was 90 and 67% respectively [Kitamura 1996]. The divergence in patency rates between the two vessels is believed to be primarily due to the saphenous vein’s propensity for developing atherosclerosis or
‘vein graft disease’ [Suma 1999].

**SURVIVAL/MORBIDITY**

**Radial artery**

One of the benefits of using the radial artery as a bypass graft is that from a surgical point of view it is easily accessible. However, theoretically there are a number of risks associated with radial artery harvesting. Studies to date, however, suggest a low risk of complications. In a study of 200 patients who underwent bypass surgery with radial artery grafts 1% suffered donor site hematomas and 2% had temporary dysethesias [Sudhakar 1998] while in a series of 328 patients who had had their radial arteries harvested only 2 patients reported late hand ischemia while there was no decrease in hand strength post-surgery although scar hypersensivity occurred in 20% of the patients [Royse 1999]. In a University of Melbourne study, out of 2,417 patients who had their radial arteries removed at a hospital only two patients, both of whom suffered from scleroderma, developed fingertip ischemia while 0.4% of patients developed a major forearm hematoma [Tatoulis 1999]. Four other studies have reported no complications following radial artery harvesting [Acar 1992; Dietl 1995; Fremes 1995; Bhan 1999] indicating the safety of this procedure.

The mortality and cardiac morbidity rates associated with using the radial artery as a bypass graft are also low. A 1995 study followed up 50 patients who received radial artery grafts in addition to other conduits and reported no early or late deaths and no myocardial ischemic complications associated with the use of the radial artery [Fremes 1995]. A study of 165 patients who received radial artery grafts reported a mortality rate of 3% (no deaths were caused by radial graft failure) and found that after 14 months angina had recurred in 3% of patients (angiography indicated that the radial artery grafts were still widely patent) [Dietl 1995]. In 200 patients who underwent bypass surgery with radial artery grafts, 1% had a myocardial infarction caused by graft failure while 2 deaths were caused by co-morbid factors [Sudhakar 1998]. Finally, in a recent study of 62 patients with radial artery grafts there were no perioperative or late myocardial infarctions and no deaths [Bhan 1999]. Data is lacking, however, on the effect of radial artery
grafting on long term survival and morbidity rates.

**Internal mammary artery versus saphenous vein**

In terms of short term data, a US study analysing the Department of Veterans Affairs Cardiac Surgery Database found that over the period from October 1990 to September 1991 the operative mortality rate for patients who received internal mammary artery grafts versus those who had saphenous vein grafts was 3.2% and 6.5% respectively [Grover 1994] while Sethi and colleagues found no difference between the operative mortality rates of these two groups [Sethi 1991].

The findings of long term studies of the mortality and morbidity rates associated with internal mammary artery versus saphenous vein grafts not surprisingly have tended to mirror the findings of patency studies, showing that over time arterial grafts perform better than vein grafts. As noted previously, in 1986 Loop and colleagues reported the findings of a study in which they had compared the survival and morbidity rates of patients who received an internal mammary artery with or without a saphenous vein graft versus those who had received only a saphenous vein graft. They found that over a ten-year period those who had only had vein grafts had a 1.61 times greater risk of death, 1.41 times the risk of late myocardial infarction and 2 times the risk of cardiac reoperation compared with patients who had received internal mammary artery grafts [Loop 1986]. In 1988, a long-term, prospectively randomised study of patients with saphenous vein versus left internal mammary artery grafts to the left anterior descending coronary artery showed a mortality rate of 18% versus 8% while myocardial infarctions occurred in 20% of the vein graft group compared with 8% of the arterial graft patients [Zeff 1988]. Lastly, a 1996 study found that the 10-year overall survival and cardiac event-free rates for internal mammary artery versus saphenous vein grafts were 89% versus 80% and 84% versus 73%, respectively [Kitamura 1996].
Multiple arterial grafts

While it has been proven that the use of internal mammary artery grafts results in improved survival compared with vein grafting alone, there has been controversy over whether the use of bilateral internal mammary artery grafting further improves survival. In 1990, Fiore and colleagues found that 13 years after following up 100 patients who had received bilateral internal mammary artery grafts and a saphenous vein graft versus 100 patients who had been grafted with one internal mammary artery graft and a saphenous vein graft the survival and morbidity rates of the first group were significantly better than those of the second [Fiore 1990]. However, two later studies found the survival rates for patients with bilateral versus single internal mammary artery grafts to be comparable [Berreklouw 1995; Dewar 1995]. Recently, however, a very large, long term study by Lytle and colleagues found that patients who received two internal mammary artery grafts had a decreased risk of death, reoperation and angioplasty compared with those with only one internal mammary artery graft [Lytle 1999].

A number of groups have also begun to report the early findings of complete arterial grafting using combinations of internal mammary, inferior epigastric, gastroepiploic, and radial artery grafts [Dietl 1993; Grandjean 1996; Antona 1997]. In 1997, Weinschelbaum and colleagues reported excellent patency rates and minimal morbidity and mortality when using the radial artery combined with the left and sometimes the right internal mammary artery to achieve total arterial revascularisation [Weinschelbaum 1997]. In 1998 a University of Toronto-based study (described below) found not only an improved perioperative cardiac morbidity and mortality with the use of two arterial grafts but they also noted that patients who received a radial artery rather a right internal mammary artery as their second graft had comparable perioperative and intermediate-term cardiac morbidity and mortality rates and that radial artery grafting was associated with a lower incidence of sternal wound infection and decreased transfusion requirements [Borger 1998]. Furthermore, Bhan et al have found the mid-term results of grafting the radial artery to be comparable with that of the pedicled internal mammary artery. However, they caution that the two vessels cannot be
given comparable status until long-term results become available [Bhan 1999].

THE UNIVERSITY OF MELBOURNE EXPERIENCE

Since the 1980s, three cardiac surgical centres with links to the University of Melbourne have been at the leading edge of research into arterial revascularisation and the use of alternative graft conduits. In 1984, following concerns over the long-term patency of the saphenous vein, the University of Melbourne began to use the internal mammary artery as a first-line graft conduit and soon progressed to bilateral internal mammary artery grafting, although the saphenous vein continued to be used as a supplement when required. In 1995, the University team moved towards performing complete arterial grafting by using combinations of both radial and internal mammary arteries [Buxton 1997b]. While a single radial artery was used initially, the team soon progressed to performing bilateral radial artery grafting, Y grafting and sequential anastomoses [Buxton 1998] and have also had good results with using the right internal mammary artery as a free graft [Tatoulis 1997]. In tandem with their research into the surgical application of arterial grafts, the researchers at the University of Melbourne also began investigating a number of related issues including: the effect of radial artery harvesting on post-operative hand function [Hare 1997]; the pharmacologic management of spasm in arterial grafts [Liu 1997; Rosenfeldt 1999]; and the comparative histopathology of arterial conduits [Ruengsakulrach 1999].

While the benefits of multiple arterial grafts have been somewhat controversial, the most recent report from the University of Melbourne demonstrates the safety and efficacy of total arterial coronary revascularisation. Following up 3,220 patients who underwent complete arterial grafting between 1988 and 1998, the Melbourne group reported patency rates of 97% at 5 years for the left internal mammary artery grafted to the LAD, 89% at 5 years for the right internal mammary artery and 91% at 1 year for the radial artery, with the latest unpublished data indicating a patency rate at 10 years of 96% for the left internal mammary artery [Tatoulis 1999]. While these results are excellent the data collected on radial artery grafting is limited. As previously noted, there is a lack of
randomised, long term studies examining the patency, mortality and survival rates associated with radial artery grafting. The prospective University of Melbourne study described below is a randomised, multicentre trial that was set up in 1996 in order to assess both the late-patency and clinical effects of grafting with the radial artery versus the free right internal mammary artery and the saphenous vein.

In this study patients are randomised into two groups, the first consisting of a younger patient group who are grafted with a left internal mammary artery and a radial artery or free right internal mammary artery while the second, older group of patients receive a left internal mammary artery and a radial artery or saphenous vein graft. The collateral circulation of the hand is assessed using either the modified Allen test [Cable 1999] or by measuring the blood pressure in the fingers by photoplethysmography and any patients with abnormal results are excluded from the study. To date the study has managed to recruit 320 patients, 147 of whom have had radial artery grafts.

As previously noted, the improvement in the results of radial artery grafting since the seventies is probably due to a combination of better harvesting techniques and the use of calcium channel blockers. Accordingly, in this study the radial artery is removed using a minimally traumatic technique. The radial artery is particularly prone to vasospasm. Therefore, in order to prevent post-operative vasoconstriction, all the patients in the study are given amlodipine (Norvasc), a calcium channel blocker which has recently been shown to be one of the more potent agents in preventing radial artery spasm [He 2000]. In terms of follow up, in comparing the overall efficacy of the radial artery versus the free right internal mammary artery and the saphenous vein, this study examines both angiographic and clinical data rather than relying solely on the results of post-operative angiography.

**OTHER MAJOR RADIAL ARTERY TRIALS**

Excluding our study, there are three long term, large scale trials that we
know of that are currently investigating the comparative efficacy of the radial artery as a coronary artery graft.

At the Sunnybrook Health Science Centre at the University of Toronto, Stephen Fremes and colleagues have been conducting a comparative radial artery graft patency study since 1992. The study is a multicentre, randomised trial and its aim is to determine the long-term patency of radial, saphenous vein and internal thoracic artery grafts 5 to 10 years postoperatively. To enter the study patients must have graftable triple vessel coronary disease, an LVEF > 35% and be scheduled solely for primary coronary artery bypass surgery. Five hundred and sixty patients are to be recruited into the study. Follow-up currently consists of angiography which is performed 7 to 12 months postoperatively although the study also plans to assess long-term patency (5 to 10 years postoperatively). Like our study, then, the Sunnybrook trial aims to investigate the long-term, comparative patency of radial artery, internal mammary artery and saphenous vein grafting. In contrast, however, in this trial the patients serve as their own control while no data has been collected on clinical (as opposed to purely angiographic) outcomes.

THE UNIVERSITY OF MELBOURNE STUDY

AIM

The primary aim of the project is to compare the patency of the radial artery (RA) when used as a coronary artery bypass graft with that of the free right internal mammary artery (FRIMA) and the saphenous vein (SV). The rates of patient survival, relief from angina, freedom from myocardial infarction and cardiac failure, and the frequency of re-operation in the different patient groups will be compared.

HYPOTHESES

- The radial artery is superior to the long saphenous vein when used as a
coronary artery bypass graft.

➢ The radial artery is superior to the free right internal mammary artery when used as a coronary artery bypass graft.

**ENTRY CRITERIA**

➢ The patient is scheduled for primary coronary artery bypass surgery alone.

➢ The patient requires more than 1 graft, that is, there are at least 2 coronary artery stenoses of $\geq 70\%$.

**GENERAL EXCLUSIONS**

➢ Renal disease with a creatinine $>0.30$ mmol/L.

➢ Chronic heart failure (NYHA Class III or IV or ejection fraction $< 35\%$ on angiography or radionuclide ventriculography).

➢ Associated major illnesses e.g., malignancy.

➢ Body mass index (BMI) $> 35 : weight (kg)/height(m^2)$.

➢ Acute presentation, that is, those patients who have an acute myocardial infarct within one week prior to surgery or who present with cardiogenic shock.

➢ Technical exclusions e.g., sequential grafting.

➢ Failure to obtain informed consent.

**SPECIFIC EXCLUSIONS**
RANDOMISATION GROUP 1 - Radial Artery or Free Right Internal Mammary Artery

- Failure to be able to use the radial artery because of an abnormal Allen Test (> 10 seconds) or abnormal digital/brachial index (< 0.8).

- Failure to be able to use the free right internal mammary artery due to, for example, previous chest trauma.

- FEV$_1$ < 50% of expected value.

- Diabetics > 60 years.

- Other patients > 70 years.

RANDOMISATION GROUP 2 - Radial Artery or Saphenous Vein Graft

- Failure to be able to use a radial artery because of an abnormal Allen test (> 10 seconds) or an abnormal digital/brachial index (< 0.8).

- Failure to be able to use the saphenous vein – e.g. due to varices, past trauma.

- Diabetics ≤ 60 years.

- Other patients ≤ 70 years.

CORONARY ARTERY EXCLUSIONS

- Diameter < 1.5mm

- Stenosis < 70%

- Diffuse Disease
GRAFT EXCLUSIONS

- Luminal narrowing > 20%
- Atherosclerosis
- Calcification (except mild / focal)
- Wall thickness > 1mm
- Diameter < 1.5mm or > 5mm

RANDOMISATION

Randomisation will be organised and supervised by Dr Ian Gordon, Statistical Consulting Centre, University of Melbourne.

RANDOMISATION GROUP 1: Radial Artery or Free Right Internal Mammary Artery

- Patients < 70 years
- Diabetic patients < 60 years

<table>
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<th>Coronary Artery Graft</th>
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<th>Subsequent</th>
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<tr>
<td>Current Operation</td>
<td>LIMA</td>
<td>RIMA</td>
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<td>Study Operation</td>
<td>LIMA</td>
<td>RA/RIMA</td>
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RANDOMISATION GROUP 2: Radial Artery or Saphenous Vein Graft

- Patients ≥ 70 years
- Diabetic patients ≥ 60 years

<table>
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<th>Coronary Artery Graft</th>
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<td>Current Operation</td>
<td>LIMA</td>
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<tr>
<td>Study Operation</td>
<td>LIMA</td>
<td>RA/SV</td>
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CONDUIT ASSESSMENT

Radial Artery

The ability to use the radial artery safely as a graft will be judged by a normal Allen test (return of circulation to the hand in ≤ 10 seconds with radial artery occlusion), or by normal digital/brachial systolic blood pressure index (≤0.8).

The radial artery is satisfactory for use as a bypass graft if it measures ≥ 2 mm. The radial artery will not be used in patients with proximal subclavian artery disease where the systolic brachial artery pressure on the affected side is 20 mmHg lower than that on the opposite side.

Saphenous Vein

The saphenous vein may be used as a coronary artery bypass graft if it is without varicities, gross wall thickening or atheroma, and peripheral pulses are present. In the absence of peripheral pulses, the saphenous vein may be used as a graft if the leg/arm Doppler pressure ratio exceeds 0.7.
Internal Mammary Artery

The internal mammary artery is satisfactory for use as a bypass graft if it measures $\geq 1.5$ mm in diameter and the flow rate is $> 60$ ml/min.

At the time of operation, if the study vessel is found to be clinically unsuitable by the surgeon, it will not be used.

SURGICAL TECHNIQUES

Internal Mammary Artery Dissection

The Left Internal Mammary Artery

The left internal mammary artery is mobilised as a pedicle with its adjacent veins, fascia, pleura and connective tissue. Side branches are clipped close to the IMA and divided with diathermy. Large branches are divided between hemoclips. The distal extent includes the bifurcation into the musculophrenic and the superior epigastric branches. Superiorly, the IMA is mobilised to the inferior border of the subclavian vein so that the pedicle is free to lie medial to the lung near the hilum.

The Right Internal Mammary Artery

The harvesting of the right internal mammary artery must be performed by the senior surgeon. The technique proceeds as for the left internal mammary artery. After mobilisation up to the inferior border of the right subclavian vein, the lower end of the pedicle is displaced medially and the mediastinal pleura divided over the lateral side of the pedicle to display the internal mammary vein (IMV), internal mammary artery and the phrenic nerve. The IMV is divided between large Weck clips. The upper right internal mammary artery is isolated and divided at the lower border of the right subclavian vein resulting in a free graft.

Vasodilatation

Five ml of a solution of Papaverine 60 mg in 100 ml of Ringer’s lactate solution and 60 ml of whole blood containing 1000 IU Heparin is injected into the
distal IMA and the IMA clipped. Blood flow of greater than 60 ml per minute and a mean arterial blood pressure of 60 mmHg are required for use of the internal mammary artery as a graft.

**Radial Artery Removal**

The radial artery is removed through an incision that extends from 2 cm below the level of the elbow to 2 cm above the wrist, in the line of the radial artery. After entering the deep fascia of the forearm, the radial artery is removed together with the collateral veins. Meticulous dissection is performed without touching the radial artery. The wound is irrigated with a solution of either papaverine or milrinone. The branches of the radial artery and associated veins are divided between Weck clips. 2 cm above the wrist, the venae comitante are separated from the radial artery and ligated with clips. The artery is also ligated at that level. The radial artery is dilated with intraluminal papaverine or milrinone $10^{-3}$M and the distal end of the radial artery is clipped. The dissection is continued up to the level of the bifurcation of the brachial artery or 2 cm below the elbow, at which site the artery is again separated from the veins and clipped proximally with medium Weck clips. The radial artery is stored at room temperature in a solution of 50% heparinized blood and 50% papaverine in Ringer’s lactate until implantation.

**Harvesting of the Saphenous Vein**

This is performed through an incision along the medial aspect of the calf extending to less than 2 cm above the medial malleolus. The saphenous vein is removed and the side branches ligated carefully with silk or with metal clips. The wound and vein are irrigated with papaverine or milrinone. The vessel is stored in the same solution of milrinone or papaverine with 50% blood.

**Coronary Artery Bypass Grafting Technique**

All anastomoses must be performed by the senior surgeon. The chest is opened through a median sternotomy. The patient is placed on cardiopulmonary bypass by cannulating the aorta, right atrium and inferior vena cava. The patient’s temperature is lowered to 34$^\circ$C. A separate cannula is placed in the
coronary sinus for retrograde coronary perfusion. The aorta is clamped and blood cardioplegic solution is introduced initially into the aortic root and subsequently via the coronary sinus to maintain cardiac arrest. Proximal and distal anastomoses are performed under aortic cross clamp. The left IMA is anastomosed to the left anterior descending coronary artery (LAD) if ≥ 1.5 mm, or to the largest artery requiring grafting. The study graft is anastomosed to an artery with a stenosis of ≥ 80%. The proximal anastomosis is marked at the aorta with 2 medium Weck hemoclips for identification in future angiograms. At the end of the procedure, the patient is rewarmed to 37°C.

**Histopathology**

A 5mm segment of the distal study artery is removed prior to implantation. This specimen is distended with blood and placed in 4% formalin for histopathological examination. These results will be correlated with graft occlusion.

**POST-OPERATIVE MANAGEMENT**

**Vasodilator Therapy**

All patients in the study are commenced on milrinone intra-operatively. Before release of the aortic cross clamp milrinone 25 mcg/kg is given over 15 minutes followed by 0.25 mcg/kg/min for up to 18 hours post-operatively, until the administration of amlodipine (see below). In patients with an elevated creatinine the milrinone dose may be reduced. Milrinone may be discontinued if the mean blood pressure (BP) < 70 mmHg, cardiac index >3 L/min/m² or systemic vascular resistance index (SVRI) < 1200 dynes/sec/cm⁵. Alternate regimes such as glyceryl trinitrate/sodium nitroprusside infusions may be used.

**Calcium Channel Blockers**

All patients in the study are commenced on amlodipine. Amlodipine (Norvasc) 2.5 mg orally is commenced the first post-operative day after the discontinuation of milrinone. The dose is then increased to 5 mg daily on the second post operative day if tolerated; i.e. if the systolic blood pressure > 100
mmHg and Norvasc can be tolerated in combination with other cardiac drugs. Norvasc is continued for a minimum period of six months.

**NB. Vasodilator therapy is commenced on all patients in the study including those in the control groups.**

**PRIMARY END POINTS**

1. **Graft patency**

   Graft patency will be assessed by angiography of all grafts. As the most important data will occur in the late part of the study, the schedule for catheterisation is as follows:

   - 10% of patients during the first month.
   - 10% of patients at 2 years.
   - 20% of patients at 5 years.
   - 30% of patients at 7.5 years.
   - 30% of patients 10 years.

2. **Clinical**

   - Onset of ischaemic chest pain.
   - Acute myocardial infarct.
   - Re-operation for coronary artery bypass grafting.
   - Death.
SECONDARY END POINTS

1. Morbidity from saphenous vein removal compared with morbidity from radial artery removal.

2. Quality of life will be assessed using the Hare/Davies Cardiac Depression Score.

STATISTICAL ANALYSIS

Graft patency and survival analysis will be performed using the Kaplan Meier technique and differences assessed using the log rank statistic. The threshold of statistical significance is confirmed at $p < 0.05$.

Power Calculation

To detect a difference of 10% between the two groups, at the 5% level of significance, power calculations suggest that 402 patients are required in each group (where the power is 80%).

Survival Data and Post-operative Assessment

Patients will be reviewed annually by their surgeon, this will include a clinical assessment and collection of survival data. Patients will be contacted every six months by the study co-ordinator. Time related comparisons will be made of survival and freedom from angina or myocardial infarction, freedom from re-operation and actual survival between patients having a radial artery graft and the control graft.
COMMITTEES

Each committee will meet every twelve months.

Steering Committee

1. Professor Brian Buxton, Director of Cardiac surgery, Austin & Repatriation Medical Centre

2. Professor Andrew Tonkin, Director of Health, Medical and Scientific Affairs, National Heart Foundation

3. Professor John McNeil, Epidemiologist, Monash University

4. Associate Professor Franklin Rosenfeldt, Head Cardiac Surgical Research Unit, Baker Medical Research Institute, Alfred Hospital

Patient Safety Committee

1. Mrs. Lyn Roberton, Patient Advocate, Austin & Repatriation Medical Centre

2. Dr Rinaldo Bellomo, Department of Intensive Care, Austin & Repatriation Medical Centre

3. Dr Laurie Doolan, Director of Operating Suite, Austin & Repatriation Medical Centre

4. Mr. A C Wilson, Director Cardiac Surgery, St Vincent’s Hospital

Data Management Committee

1. Dr Ian Gordon, Statistical Consulting Centre, University of Melbourne

2. Professor Brian Buxton, Director of Cardiac surgery, Austin &
3. Ms Kathleen Cowie, Research Co-ordinator, Department of Cardiac Surgery, Austin & Repatriation Medical Centre

4. Dr Jai Raman, Cardiac Surgeon, Austin & Repatriation Medical Centre

5. Dr John Fuller, Victorian Heart Centre, Epworth Hospital
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Chapter 10
Summary

RESULTS OF HYPOTHESIS TESTING

First hypothesis: Suitability
Second hypothesis: Safety
Third hypothesis: Efficacy

CONCLUSIONS
RESULTS OF HYPOTHESIS TESTING

In this thesis, I have addressed three main concerns in relation to the role of the radial artery (RA) as a coronary artery bypass graft, namely the question of its suitability, its safety and its efficacy.

First hypothesis: Suitability

In Chapter 2, I argued the suitability of the RA as an alternative to other graft conduits by demonstrating the ease with which this vessel can be accessed and harvested. I also documented the important variations of the forearm and hand arteries, defined the possible anatomical connections between the radial and ulnar arteries in the hand, and demonstrated the safety of RA harvesting by showing that it is very unusual for a hand not to possess some degree of collateral circulation. All the hands examined in my study had at least one artery supplying the thumb either via the ulnar dominant type or through the deep palmar arch and there was no hand with an ulnar non-dominant superficial palmar arch and an incomplete deep palmar arch. However, at the same time I emphasised the fact that it is common for patients requiring coronary artery surgery to have multiple sites of vascular disease such as carotid disease, aortoiliac disease and femoropopliteal disease. I therefore emphasized the importance of considering vascular pathology in the arm, forearm and hand arteries when harvesting the RA.

In order to further assess the suitability of the RA as a bypass graft, in Chapter 3 I described the histology and histopathology of the artery. In Chapter 4, I discussed a study performed by myself and colleagues in which we sought to investigate the histopathology of the RA by comparing radial arteries sampled from patients who underwent coronary artery bypass grafting with the internal thoracic artery, the standard conduit for grafting. I found that the RA had a much higher rate of intimal hyperplasia and atherosclerosis than the internal thoracic artery, both in relation to prevalence and severity indices such as the percentage of luminal narrowing, the intimal thickness index and the intima-to-media ratio. On the basis of our histopathologic study, I believe that most radial arteries are suitable as a graft. However severe disease present in a minority of vessels might compromise long-term
graft patency. The RA therefore needs to be selected carefully before being used as a graft. My studies indicate the necessity for applying considerable caution in using the RA in patients with aortoiliac disease, in diabetic patients who are 63 or older, and in those aged $\geq 78$ without diabetes.

These findings highlight the importance of determining a way of identifying disease-free radial arteries prior to surgery. Accordingly, in Chapter 5 I examined the efficacy of ultrasound for preoperatively screening the RA for calcification and intimal hyperplasia and found that ultrasound had a diagnostic accuracy rate of 85% for detecting calcification in the RA. It should be noted that while it is recommended not to use the RA when it is calcified there are some concerns that ultrasound is not able to distinguish between atherosclerosis calcification from medial calcification. There is a lack of data on the effect of medial calcification on graft patency. To answer this question, long-term follow up of patients whose grafted RA show medial calcification is required. Even though ultrasound was not useful for evaluating the degree of intimal hyperplasia in the RA, it can be employed to evaluate the luminal diameter of the RA with reasonable reliability. Accordingly, I concluded that ultrasound is a useful tool for screening for disease in the RA. However, further development of ultrasound techniques and technology is needed in order for it to accurately detect the degree of intimal hyperplasia in the RA.

**Second hypothesis: Safety**

A major concern about RA grafting is whether or not RA harvesting is a safe procedure. To determine this, I evaluated three tools for preoperatively assessing the RA and the collateral circulation of the hand. The first screening test examined was the modified Allen test, a procedure that can be performed by the bedside without any sophisticated equipment. In chapter 6, I confirmed the advantage of using the modified Allen test by comparing it with Doppler ultrasound. An abnormal Doppler dynamic test occurred when there was no flow in the thumb with RA occlusion and this indicated that if the RA was harvested, there is a high risk of hand ischemia. Compared with the Doppler dynamic test, the modified Allen test accurately detected poor collateral circulation in the hand. The modified Allen test was also easier to conduct. In Chapter 7, I discussed a study undertaken by colleagues and myself in
which we used the thumb brachial index with RA occlusion measured by photoplethysmography as a baseline against which to compare the accuracy of the modified Allen test. The modified Allen test correlated well with the thumb brachial index with RA occlusion. The diagnostic accuracy of the modified Allen test was 82%. One of the problems I faced was identifying an appropriate cut-off point for the modified Allen test which would indicate that a patient was at risk of ischemic complications following RA harvesting. To be conservative, we used a recovery time of 8 seconds as a cut-off point with a sensitivity rate of 82% and specificity rate of 80% compared with the thumb brachial index with RA occlusion.

**Third hypothesis: Efficacy**

In Chapter 8 and 9, the efficacy of the RA for use as a bypass conduit for CABG was tested. The survival rate of patients using the RA as a second graft in addition to the left internal thoracic artery was comparable with the survival rate of patients using both left and right internal thoracic arteries in an average three-year follow-up. Survival was better than in patients where the saphenous vein was used with the left internal thoracic artery. This study included a wide spectrum of patients, however it was an observational study subjected to bias of graft selection by surgeons. In Chapter 9, semi-quantitative and quantitative coronary angiography in a prospective randomized controlled trial demonstrated that at one year, in younger patients (≤70 years without diabetes and ≤60 years with diabetes), the RA grafts had a similar diameter and area stenosis compared with the right internal thoracic artery. In older age patients (>70 years without diabetes and >60 years with diabetes), the RA grafts demonstrated less stenosis than saphenous vein grafts. However these preliminary results involved a very small number of patients, which is a limitation.
CONCLUSIONS

Overall in my thesis, I concluded that the RA grafting is safe and the RA is a potentially effective alternative conduit for coronary artery bypass grafting. The RA showed higher prevalence and severity of intimal hyperplasia and atherosclerosis than the internal thoracic artery but the diameter loss was still relatively low. The early survival rate in patients having a RA graft as a second conduit were comparable with those receiving a right internal thoracic artery. The early result also suggested that the survival rate was better than those patients having a saphenous vein. In order to investigate the effect of pre-existing disease processes on the RA graft patency, a long-term follow-up study with graft angiography is required. A prospective randomised study to assess the relative graft patency of the RAs, right internal thoracic arteries and saphenous veins more conclusively is currently underway.
Chapter 11
Future

FUTURE DEVELOPMENTS

(a) Laboratory Experimental Trials
(b) Clinical Trials

GENE THERAPY

SYNTHETIC CONDUITS

SURGICAL TECHNIQUES
FUTURE DEVELOPMENTS

In this section, some of the questions left unanswered in my thesis will be briefly discussed. Possible future approaches to these issues will also be explored.

(a) Laboratory Experimental Trials

I have shown that some radial arteries demonstrate a high degree of intimal hyperplasia. Low-density lipoprotein (LDL) preferentially accumulates at sites of intimal thickening in human arteries.\textsuperscript{328} It has been shown that the RA produces less endothelial relaxing factors compared with the internal thoracic artery suggesting diminished endothelial regulation of vascular smooth muscle in the RA.\textsuperscript{329} Thus the RA may be prone more to spasm than the internal thoracic artery. Endothelial injury during harvesting and surgical preparation of the graft,\textsuperscript{330} together with the decreasing of nitric oxide and prostacyclin production from endothelial dysfunction permit platelet adhesion and aggregation.\textsuperscript{331} This is followed by stimulation of vascular smooth muscle cells to proliferate and to migrate to the intima. The smooth muscle cells undergo a phenotypic change from contractile to secretory cells, and extracellular matrix accumulates. Platelet activation provokes the release of platelet-derived growth factor and basic fibroblast growth factor. These processes might result in flow limiting intimal hyperplasia in the graft. This intimal hyperplasia consists of secretory vascular


smooth muscle cells and extracellular matrix. It must be noted that most of these studies were based on saphenous vein models.

Thus, to prevent RA graft failure, we need to understand the pathophysiologic changes of the arterial conduit occurring after implantation into the coronary system, develop different methods for prevention of each step leading graft failure. The methods that might be used to study arterial graft failure can be taken from the models of vein graft failure suggested by Baker and colleagues.332

1. *In Vitro: The human artery organ culture model*

The advantage of this *in vitro* model is that the use of human endothelia produces results which can be applied directly in humans. The aim would be to compare the difference between neointimal formation in arterial versus vein grafts, and to identify a number of genes important to neointimal development including platelet-derived growth factor (PDGF) and its receptors, metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases (TIMPs). This model also offers the potential for further research into gene therapy.

2. *In Vivo: The porcine model of arterial interposition grafting*

This *in vivo* experimental model would allow examination of the free arterial graft compared with the pedicled arterial graft in terms of both physiologic and pathologic changes. The advantage of an *in vivo* model is that the graft is exposed to an active physiological environment consisting of arterial hemodynamics and circulating blood products (cells, hormones, coagulation

factors etc.). Even though this would be an animal study, the pig shares a similar coagulation profile and lipoprotein metabolism to that of humans and is susceptible to spontaneous and diet-induced atherosclerosis. Of the other animal groups, only primates show such similarities, but their use is limited by their higher cost and special handling requirements.

In this study, we could examine the differences between T, Y and end-to-end (extension) grafts in order to provide scientific evidence for the expanded use of arterial conduits including the RA. The hypotheses would be that the primary pedicled graft has less neointimal formation than the graft extension, the graft extension has less neointimal formation than the Y graft and the Y graft has less neointimal formation than the T graft.

(b) Clinical trials

Another important question raised by the histopathologic analysis relates to the effect of pre-existing intimal disease on graft patency. To date, most investigators have assumed that intimal hyperplasia is a sign of pathology and is the first step in atherogenesis. However intimal hyperplasia may develop as an adaptive response to physiologic stimuli. Cable and colleagues studied the development of intimal hyperplasia in human saphenous veins, internal thoracic arteries and RAs in an organ culture with Rosewell Park Memorial Institute 1640 (30% serum) for 0, 4, 7, 10 and 14 days. The intima-to-media ratio using quantitative histological studies was significantly increased in the saphenous vein after 10 and 14 days of culture and not significantly increased in the internal thoracic arteries and RAs. Questions arising thus are: (1) Does intimal hyperplasia increase after aortocoronary bypass?; and (2) Does the pre-existing degree of intimal hyperplasia affect the graft patency? Given that the development of graft atherosclerosis is a long and slow process, such a study would need to be long-term (perhaps 5-10 years). Quantitative coronary angiography is needed to examine the correlation between the degree of pre-existing intimal hyperplasia,

progression of intimal hyperplasia and graft patency. To examine this issue, a study has been organized in which my colleagues and I will follow up 184 patients who have had histopathologic examination of their radial arteries, and we will correlate the histopathologic findings with long-term clinical outcome and graft patency. The hypothesis is that the radial arteries which had a higher degree of intimal hyperplasia pre-implantation will be associated with a poor outcome and lower graft patency rate. If a relationship between the degree of intimal hyperplasia and subsequent poor graft performance is proven the next step would be to attempt to minimize the intimal hyperplasia process early on through blockade of growth factors e.g. using ACE inhibitor or the future development of gene therapy.

The randomized studies comparing the RA with the saphenous vein and the free internal thoracic artery are mentioned in Chapter 9. The end points of this study are the clinical and angiographic findings and require a longer-term follow-up.

**GENE THERAPY**

The Human Genome Project began in the United States in 1989, has been completed. The aim of this project was to map or locate the complete nucleotide sequence of human DNA. With the genetic map available it becomes possible to manipulate genes thus creating a whole new research area as well as tremendous future applications for what is known as “gene therapy”.

Molecular biology has made a number of recent advances in the field of cardiovascular medicine. For example, in the area of congenital heart disease, recent breakthroughs in the understanding of the regulation of genetic markers associated with cardiac chamber formation and specification, combined with insights into the molecular switches that regulate the expression of these markers, are beginning to provide a foundation for the analysis of the complex process of cardiogenesis. In this area, the study of the *in vitro* differentiation of totipotent mouse embryonic stem cells into cardiac muscle cells with ventricular specific properties, may ultimately allow investigators to examine the early process of
chamber specification in genetically engineered cardiac muscle cells. As the factors that play roles in cardiac expression become identified, gene knockouts of these candidate loci may uncover connections with specific congenital defects in humans - a long awaited event in the field.

To date, gene therapy has been used for the treatment of ischemic heart disease in three areas: (1) graft modification; (2) angiogenesis; and (3) xenotransplantation. Research has also been commenced on the prevention of angioplasty restenosis and in gene therapy for hypercholesterolemia and hypertension.

In terms of the prevention of coronary artery bypass graft failure, one of the major drawbacks in the use of gene therapy has been the problem of gene delivery. Two delivery systems have been used to insert genes into cells: (1) non-viral and (2) viral. Non-viral methods include calcium phosphate, dithyl-aminoethyl (DEAE)-dextran and liposome mediated gene transfer. Viral methods include retroviruses, adenoviruses, herpes viruses, lentiviruses and parvoviruses. The major limitation of these delivery systems is that a number of these methods have proved unable to induce high efficiency gene delivery in vivo. Baker and associates in 1997 recommended the use of recombinant adenoviruses as the most efficient delivery system in which high level transient gene expression can be achieved in vitro and in vivo. They have the ability to infect both dividing and non-dividing cells. The lack of viral DNA integration into the host genome results in transient recombinant gene expression. A major problem with the use of adenoviral gene delivery systems is the host inflammatory response to infected cells induced in vivo. This can lead to the elimination of infected cells in vivo and hence, a rapid decline in the level of transgenic production. Subsequently, the adenoviral genome has been modified in an attempt to eliminate or substantially reduce the immune response evoked. Further development and evaluation of these systems in vivo will determine their applicability for use in clinical gene therapy.

Another limitation of gene therapy for the prevention of graft failure is that the expression of factors inhibiting platelet activation or adhesion may reduce early graft failure transiently during gene expression provided by most vectors. It is also unknown whether early transient gene expression can provide long-term benefits, such as the prevention of late graft failure. Unlike restenosis, where the injury is brief and the response occurs relatively rapidly, the stimuli for smooth muscle cell proliferation in grafts (shear stress, tangential wall stress, etc) persist long after graft implantation and thus may require prolonged expression of a given therapeutic gene. The antiproliferative gene transfer technology that has been used to prevent smooth muscle cell proliferation includes (1) the cytotoxic approach involving the transfer of the viral thymidine kinase (TK) gene and the systemic delivery of the pro-drug ganciclovir to induce cell death, (2) the cytostatic approach, and (3) the diffusible inhibitor approach which involves the gene transfer of the endothelial form of nitric oxide synthase complexed to the Sendai virus-liposome complex. The latter approach has demonstrated a reduction in restenosis of 70% in a rat carotid injury model. Like the cytotoxic approach, this requires lower transduction efficiency than cytostatic strategies as the nitric oxide produced from transduced cells produces a bystander effect on non-transduced cells. In addition to these approaches, several other experimental mechanisms for the prevention of graft failure have been investigated. These included the adenoviral-mediated gene transfer of the tissue inhibitor of metalloproteinases (TIMPs) to the vessel wall, the adenoviral-mediated gene transfer of COX-1 in order to augment prostaglandin I2 synthesis and the gene transfer of a soluble vascular cell adhesion molecule (sVCAM) in order to block monocyte binding to the vascular endothelium through competitive inhibition of binding to wild type, cell surface associated VCAM.

Cable and colleagues demonstrated adenoviral-mediated gene transfer of bovine endothelial nitric oxide synthase inhibition of intimal hyperplasia in the human saphenous vein in vitro.\textsuperscript{336}

The transcription factor E2F regulates the expression of several genes involved in the progression of G1/S transition and DNA replication in mammalian cells. The ability to inhibit transcription by blocking E2F expression has great potential in the treatment of proliferative disorders.\textsuperscript{337} The effect of double-stranded phosphorothioate oligonucleotides containing E2F transcription factor cis element, a so called 'decoy' has examined on the growth of cultured human cells and the intimal hyperplasia in vessels. In 1999, Mann and colleagues performed a prospective, randomised, double blind in 41 patients underwent infrainguinal arterial bypass grafting using E2F decoy oligodeoxynucleotide, delivered by a novel method of pressure-mediated DNA transfection into human vein grafts that does not require viral or exogenous lipid formulations.\textsuperscript{338} Fluorescent microscopy of vein transfected with fluorescein-isothiocyanate-labelled oligodeoxynucleotide showed successful delivery and nuclear localization in a mean of 89.0\% (SD 1.9) of cells throughout the vessel wall. The expression of proliferative-cell nuclear antigen and \textit{c-myc} was lower in vein segments transfected with E2F decoy oligodeoxynucleotide than in segments of untreated veins from the same patients. At 12 months, fewer graft occlusions, revisions, or critical stenoses were seen in the E2F-decoy group than in the untreated group (hazard ratio 0.34 [95\% CI 0.12-0.99]). Primary patency also continued to decline in the untreated group compare with E2F-decoy group after


six months follow-up. This result was confirmed in animal models. A single intraoperative pressure-mediated delivery of E2F decoy effectively provides vein grafts an inhibition of neointimal hyperplasia and atherosclerotic plaque formation and remained stable throughout the 6 months of cholesterol feeding.

Kawauchi and colleagues tested the efficacy of double-stranded DNA with specific affinity for E2F (E2F decoy) in preventing intimal hyperplasia using ex vivo single intraluminal delivery of E2F decoy into cardiac allografts of mice and Japanese monkeys using the hemagglutinating virus of Japan (HVJ) artificial viral envelope-liposome method. E2F decoy prevented neointimal formation and suppressed these genes for up to 8 weeks and neither complication nor dissemination of HVJ into other organs was observed.

SYNTHETIC CONDUITS

Three types of synthetic conduits have been developed: (1) polytetrafluoroethylene (PTFE) graft; (2) Perma-Flow graft; and (3) autogenous endothelial cell seeded graft.

The PTFE graft, 4 mm in diameter, has been used in a number of patients who had no suitable alternative conduit. In early experience, patency rates were reported to be 60% at one year but only 14% at 45 months in early experiences.

The Perma-Flow prosthetic coronary graft designed as an arteriovenous configuration was developed in North America. The graft was constructed


proximally at the aorta, end to side, and then sequentially anastomosed side to side to the coronary arteries. The distal end of the graft was anastomosed to the superior vena cava. The graft was incorporated with a Venturi flow restrictor, which controlled the flow maintaining arterial pressure proximally and venous pressure distally. Scheduled coronary angiograms in 28 patients one week to one year postoperatively demonstrated that seven of 73 studied coronary anastomoses (9.5%) and two distal extensions and restrictors (7%) were occluded.342

Advances in molecular biology have led to the development of a promising alternative conduit in which the surface of a synthetic prosthesis is subjected to endothelial seeding. In a report from Germany, graft patency was 90.5% at an average of 27.7 months follow-up (range, 7.5 – 48 months) in 14 patients with 21 autogenous endothelial cell-seeded 4 mm polytetrafluoroethylene grafts.343

It is possible that continued development of prosthetic grafts would provide an unlimited source of conduits with excellent long-term patency.

**SURGICAL TECHNIQUES**

Apart from vascular graft development, surgical techniques have been modified. The minimally invasive coronary artery bypass grafting (CABG) has become popular. Modified skin incision techniques include minimally invasive direct coronary artery bypass (MICAB)344, lateral anterior sternotomy

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technique\textsuperscript{345}, Transabdominal CABG\textsuperscript{346}, Port-access CABG\textsuperscript{347}, Endoscopic CABG\textsuperscript{348} and Robotic CABG\textsuperscript{349}. All of these techniques must combine with surgery without cardiopulmonary bypass (Off-pump) or modified cardiopulmonary bypass techniques. The advantage of Off-pump CABG is it avoids neurological deficit including neurocognitive dysfunction, transient neurological deficit and stroke.\textsuperscript{350} In addition Off-pump surgery also avoids the


cardiopulmonary bypass and cardioplegic arrested heart which stimulate systemic inflammatory responses and endothelial dysfunction.\textsuperscript{351} The issue of the reduction of the inflammatory response using Off-pump CABG technique is controversial.\textsuperscript{352}

Off-pump CABG was performed originally in experimental surgery in the 1970s. In 1972, Ankeny reported CABG without cardiopulmonary bypass in 143 patients at The Society of Thoracic Surgeons.\textsuperscript{353} In 1975 Trapp and Bisarya reported an Off-pump CABG in 63 patients.\textsuperscript{354} In 1982, Buffolo and colleagues reported their Off-pump CABG technique.\textsuperscript{355} In 1984, Akin and colleagues reported an abnormal septal motion in patients having CABG with cardiopulmonary bypass compared with Off-pump CABG.\textsuperscript{356} In 1985, Buffolo and colleagues presented the results of 160 patients who underwent Off-pump CABG.\textsuperscript{357} The distal sutures were performed with interruption of the coronary flow without any devices for perfusion of the coronary artery: the proximal sutures were performed with tangential clamping of the aorta. Hospital mortality was 3.1\% and perioperative myocardial infarction 2.5\%. Postoperative angiography in 41 of the 160 patients (25.6\%) showed a patency rate of 83.9\% in the 62 grafts restudied. In 1985, Benetti reported his good result of Off-pump


CABG in 30 selected patients between October, 1980 and April, 1983.\textsuperscript{358} Larger series were reported with a good outcome in experts’ centre and selected patients.\textsuperscript{359} Gundry and colleagues, based on their experience from June 1989 to July 1990, raised the issue of the quality of the anastomoses.\textsuperscript{360} One hundred and seven patients underwent Off-pump CABG and 112 patients revascularization with the aid of bypass with cardioplegia. Mean ages (65 +/- 10 years) and risk factors were identical. Patients operated on with the heart beating had 2.4 ± 0.9 grafts versus 3.2 ± 1.1 for patients having cardiopulmonary bypass. They found that despite one less graft per patient, survival and cardiac death rates were similar for the two groups. However, twice as many patients in the Off-pump CABG group required recatheterization (30% versus 16%) and 20% needed a second intervention. Only 7% of the bypass with cardioplegia group required reintervention.

In 1996, Borst and colleagues assessed the feasibility of coronary artery bypass grafting on the beating heart with a suction of stabilizer “Octopus” in 31 pigs.\textsuperscript{361} They studied the motion of the epicardium and anastomoses using “Octopus”. The motion was about 1 \times 1 mm and anastomoses can be performed without adverse consequences.


In 1997, Jansen and colleagues reported results of Off-pump CABG using “Octopus” stabiliser in 27 patients. Surgical access was achieved via a 10-cm anterior thoracotomy (n = 26) or 10-cm subxiphoid incision (n = 1). Immobilization with the “Octopus” was effective and facilitated precise anastomosis suturing of 20 single and 7 sequential grafts. Immobilization did not change cardiac index and mean arterial blood pressure. During coronary surgery, however, inotropic drug support was used in 5 of 27 (18%) of patients. There was no myocardial infarction. At 6 months angiography was performed in 15 of 27 patients. The patency rate of 19 of 20 anastomoses was 95%. This technique was expanded to use for revascularization at the posterior wall of the left ventricle.

In 1997, Suen and colleagues reported results in 32 patients of Off-pump CABG via a small anterior thoracotomy. Twenty, five, and seven patients had one, two and three vessels diseased respectively. One patient required intra-operative conversion to conventional CABG for an intramyocardial target vessel. Two patients had conversion after post-operative angiogram demonstrated incorrect target identification and early graft occlusion. Four patients had limited access graft revision (two kinks, one graft injury, and one hemorrhage). Thirty-one of the 32 patients were followed from 0.5 to 16 months with 30 reporting no post-operative cardiac events (one required PTCA to another vessel). In 1997, Carrier and colleagues quantitatively evaluated coronary anastomoses with Off-

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pump CABG in 19 patients.\textsuperscript{365} Twenty ITA grafts and seven saphenous vein grafts were studied by quantitative angiography in the immediate postoperative period (4 ± 2 days). Diameter stenosis of the native coronary artery averaged 19 ± 26% proximal to the anastomosis, 36 ± 31% distal to the anastomosis and 27 ± 32% at the anastomotic site of ITA grafts. One native coronary artery distal to the anastomosis was occluded and an occluded anastomosis was reopened by percutaneous angioplasty 72 h after surgery. Saphenous vein grafted to the right coronary artery had only minimal stenosis at anastomotic sites.

In 1998, Jaber and colleagues studied the relationship of the anastomosis stenosis and graft flow in 14 mongrel dogs that underwent Off-pump CABG.\textsuperscript{366} Moderate to severe degrees of stenosis were created at the anastomosis by an additional suture. ITA graft flow was measured before and after the stenosis was created with the left anterior descending artery occluded. Postoperative angiography was performed randomly to validate the degree of stenosis. Mean flow and flow tracing morphology were compared under various degrees of stenosis. There were no significant differences in mean graft flow or the morphology of the flow tracing between patent (<15%), mild (<25%), moderate (<50%) and moderately severe (<75%) stenosis. However, mean graft flow decreased ($P < 0.05$) with severe stenosis (>75%). Jaber also conducted a survey with the cooperation of 19 international surgeons to assess the ability of surgeons to detect anastomotic errors by evaluating mean flow and flow waveform morphology.\textsuperscript{367} Responders were able to clearly identify a highly stenotic graft (>90% stenosis). However 24% would re-do a fully patent anastomosis, 58% accepted an anastomosis with moderate stenosis, and 72% accepted anastomoses with severe stenosis.


The quality assessments of the anastomoses performed using Off-pump technique have been developed.368

Several prospective randomised trials have been performed with encouraging results.369 The Off-pump technique is also being used for complete arterial coronary artery bypass grafting including bilateral ITA, RA and right gastroepiploic artery.370 In 1999, Pym reported results of total arterial grafting in 125 patients operated on between 1997 and 1998 using suction stabilizer.371 Aortic anastomoses were avoided: both ITAs and the RGEA were used as pedicle grafts in all but one case. All RAs and one right ITA were used as Y-grafts from the left ITA. Various skin incisions were used. Sternotomy incision group: 187 grafts were performed in 98 patients (mean 1.9 grafts per patient). There were 99 grafts to anterior wall vessels, 47 to posterior wall vessels and 41 to lateral wall vessels. Left anterior thoracotomy incision group: 20 patients had a single graft to the left anterior descending artery. Left anterolateral thoracotomy incision group: three patients had a single graft to a circumflex branch while three had composite grafts to the left anterior descending artery and circumflex systems. Subxiphoid incision group: one patient had a single graft to the posterior descending branch of


the right coronary artery. There were no peri-operative deaths in any group. No patient required conversion to cardiopulmonary bypass. Three patients required conversion from a limited-access approach to sternotomy. By avoiding aortic manipulation and meticulous anastomosis with pedicled and composite arterial graft, maximum benefit in terms of neurological preservation and graft patency can be achieved.

However there are several concerns about the quality of anastomoses and compromised numbers, locations and grafting techniques. For experienced surgeons, surgery will be less compromised. Learner surgeons will avoid complicated techniques such as anastomosis of pedicle left or right ITA to the circumflex system, sequential anastomoses, and proximal location of target artery. A simulated beating heart for coronary artery bypass grafting training will be useful.

Furthermore automated anastomotic devices and a nonsuturing anastomosis technique have been developed. Another area of development is the minimally invasive graft harvesting techniques such as endoscopic saphenous vein or RA harvesting. These endoscopic techniques might be able to reduce the wound complication in some patients.

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“The progression of humanity appears to us to be very slow because we, the observers, are units of the herd. Each one of us can make but few observations. Our life is too short. Many experiments should be conducted for a century at the least. Institutions should be established in such a way that observations and experiments commenced by one scientist would not be interrupted by his death. Such organizations are still unknown in the realm of science. But they already exist in the other lines of endeavor. In monastery of solemans three successive generations of Benedictine monks have devoted themselves, over a period of about fifty-five years, to the reconstruction of Gregorian music. A similar method should be applied to the investigation of certain problems of human biology. Institutions, in some measure immortal, like religious orders, which would allow the uninterrupted continuation of an experiment as long as might be necessary, should compensate for the too short duration of the existence of individual observers.”

Alexis Carrel
Man, The Unknown

“Study is continuing until the final answer is determined.”

Permyos Ruengsakulrach
June 30, 2001
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