ASSESSMENT OF OPERATIVE STRATEGIES TO IMPROVE CORONARY BYPASS GRAFT PATENCY

by

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ABSTRACT

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The ultimate success of bypass surgery depends on the construction of a technically perfect bypass graft to an appropriate coronary vessel using a conduit which will remain durable for the lifetime of the patient. This thesis explores methods to improve coronary surgery by enhancing intraoperative imaging and conduit selection in the operating room.

It is known that technical errors in graft construction cause failure of up to 12% of coronary bypass grafts in the operating room. We performed investigations of a new technique of intraoperative fluorescence angiography using indocyanine green dye to determine graft patency. We developed optimal methods of obtaining images and preliminary investigations revealed the technique was highly reproducible. In a follow-up trial, we demonstrated that over 80% of technical errors which would otherwise have been missed were identifiable with indocyanine green angiography, while only 25% of these errors were identified by transit-time ultrasonic flow measurement, the current clinical standard. We also determine that coronary surgery with indocyanine green angiographic graft patency verification was associated with less perioperative myocardial injury than bypass surgery without graft patency assessment.

The long term graft patency of saphenous vein grafts is sub-optimal, with over 40% of such grafts totally occluded and a further 30% significantly diseased at ten years. We attempted to improve these outcomes by increasing the use of arterial grafts, which are less prone to intimal hyperplasia. In a multicentre clinical trial, we demonstrated a 40% relative risk reduction in graft occlusion at one year when radial arteries were used as bypass conduits versus saphenous veins. We identified that women and patients with
small coronary vessels maximally benefited from radial artery bypass grafts. Conversely, in settings of less severe target vessel stenosis or concomitant peripheral vascular disease, saphenous veins performed as well as radial arteries.

We have demonstrated that high quality imaging to identify technical errors during the operation, increased use of radial artery grafts and careful consideration of individual patient and target vessel characteristics can all improve graft patency. Future studies will be aimed at identifying the role of intraoperative imaging and arterial grafting in improving long-term clinical outcomes.
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STUDENT’S ROLE

All the written material in this thesis was drafted in the first instance by the candidate. As per usual practices, extensive editorial input from member of the supervisor, thesis committee as well as Drs. Naylor and Cohen were given for the various chapters. For all chapters, all statistical analyses were performed entirely by the candidate with guidance from Drs. Fremen, Naylor and Kiss. All aspects of study design and implementation were performed by the candidate for all studies with the exception of chapter 6, for which Drs. Fremen, Naylor and Cohen coordinated the early design and recruitment aspects. All manuscripts derived from this thesis were drafted by the candidate with the usual input from coauthors. I am therefore able to assume full academic responsibility for the thesis and all associated manuscripts published or submitted.
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Chapter 1.

Introduction

1.1. Historical Context of Coronary Surgery

Throughout recorded history, scholars, philosophers and physicians contemplated the moral implications and scientific possibilities of touching man’s heart. The pioneers of heart surgery often had to endure the scorn of their physician colleagues, the media, and the general public. Fuelled by the urgency to save their patients, the drive for innovation, or simply unabated hubris, these surgeons attempted heroic and often misadventurous operations under the close scrutiny of their peers. The opposition to surgery on the heart by philosophers and scientists date back to the finality in the words pronounced by Hippocrates in the 4th century B.C., “A wound in the heart is mortal.”(1) Later, Aristotle asserted, “The heart alone of all the viscera cannot withstand injury. This is to be expected because when the main source of strength is destroyed there is no aid that can be brought to the other organs which depend on it.”(2) Nearly two millennia later, the 16th century French battlefield surgeon, Ambrose Pare proclaimed, “The heart is the chief mansion of the soul, the organ of vital faculty, the beginning of life, and the fountain of the vital spirits, and so consequently the continued nourisher of the vital heat, the first to live and the last to die.”(3) Such sentiments continued to echo throughout history and continued even well into the nineteenth century when the preeminent surgeon of the era, Theodor Billroth, pronounced that, “A surgeon who tries to suture a heart wound deserves to lose the esteem of his colleagues.”(4)
Initial Attempts at Coronary Revascularization

During the late 1800s, there were a few isolated reports of successful surgical repair of cardiac stab wounds using simple sutures but no intracardiac or coronary artery surgery had been attempted. (5) Future Nobel Laureate Alexis Carrel performed the first coronary bypass surgery on a dog in 1910. (6) He used a length of carotid artery to join the descending thoracic aorta to a circumflex coronary artery branch. In his words:

“I attempted to perform an indirect anastomosis between descending aorta and the left coronary artery... On account of the continuous motion of the heart, it was not easy to dissect and to suture the artery. In one case, I implanted one end of a long carotid artery, preserved in a cold storage, on the descending aorta. The other end was passed through the pericardium and anastomosed to the pericardial end of the coronary near the pulmonary artery. Unfortunately, the operation was too slow. Three minutes after the interruption of the circulation fibrillary contractions appeared, but the anastomosis took five minutes. By massage of the heart, the dog was kept alive, but he died less than two hours afterwards. It shows that the anastomosis must be done in less than three minutes.” (6)

In the 1930s, Claude Beck in Cleveland, observed in a post-mortem examination that a patient with totally occluded right and left coronary arteries had developed dense adhesions around his heart, which Beck believed arose as a response to augment
myocardial blood flow from adjacent tissue. Based on this observation, he set out to
design experiments in which adjacent tissues including pericardium, pericardial fat,
pectoralis muscle, and omentum were mobilized and wrapped around the heart.
Postmortem examination showed that anastomotic vessels did develop between these
tissues and the myocardium. In the first patient, Beck roughened the outer surface of the
heart with a burr and then sutured a pedicle graft of pectoralis muscle to the left
ventricular wall. (7) The patient made an uneventful recovery and was angina-free after
the operation. Beck performed this operation, known as the Beck I, on 16 patients with
only 4 deaths. Dwight Harken in Boston and others attempted similar procedures.
Harken, believing the epicardial layer prevented collateral formation, used 95%
carbolic acid to remove it.(8) Beck later speculated that the coronary veins may be able
to carry oxygenated blood back to myocardial tissue. Beck used a length of brachial
artery to join the aorta with the coronary sinus and then ligated the coronary sinus
where it enters the right atrium to prevent blood from flowing back into the atrium. (9)
Canadian Arthur M. Vineberg, based at McGill University in the early 1950s reported
implanting the internal mammary artery through a tunnel into the myocardium.(10;11)
He did not actually anastomose the left internal mammary artery to a coronary artery
but placed the graft directly into the muscle. Vineberg previously observed in animals
that although direct arterial implantation into skeletal muscle lead to the formation of
large hematomas, in heart muscle, this was not the case and it acted more like a sponge
with the blood distributed into channels within the muscle itself. While many surgeons
disputed this concept, Vineberg was able to show that many patients with disabling
angina were able to return to their normal lives, angina-free. Mason Sones, innovator
of coronary angiography, later validated Vineberg's concept by demonstrating communications between the graft in the myocardium and the coronary system by angiography in two patients operated on 5 and 6 years earlier. (12) In the largest follow-up series, Ochsner and colleagues showed that 31/73 internal mammary artery implants were patent and had formed collaterals to large coronary vessels at 7 to 10 year follow-up. (13)

The first known coronary bypasses on humans were performed in 1964 by Soviet surgeon V. I. Kolessov. (14) Operations were performed through a left thoracotomy without extracorporeal circulation or preoperative coronary angiography. In 1968, American surgeons George Green and Charles Bailey separately published case reports in which the internal mammary artery was used for coronary artery bypass in patients. (15;16) Bailey carried out the anastomosis on the beating heart while Green advocated using cardiopulmonary bypass and fibrillatory arrest. Rene Favalaro performed the first saphenous vein graft aortocoronary bypass in 1968. (17) W. Dudley Johnson furthered efforts to standardize coronary surgery by applying a disciplined approach which could be reliably taught to others. Johnson stated when presenting his paper,

"Our experience indicates that five factors are important to direct surgery. One: Do not limit grafts to proximal portions of large arteries.... Two: Do not work with diseased arteries. Vein grafts can be made as long as necessary and should be inserted into distal normal arteries. Three: Always do end-to-side anastomosis.... Four: Always
work on dry, quiet field. Consistently successful fine vessel anastomoses cannot be done on a moving, bloody target.... Five: Do not allow the hematocrit to fall below 35.” (18)

Coronary artery bypass grafting (CABG) is currently one of the most commonly performed major surgical procedures in the western world. CABG is now established as a highly effective treatment for complex, multivessel coronary artery disease with proven ability to improve symptoms in many patients and prolong life in selected subgroups. Advances in myocardial protection and perioperative management during the past decades have substantially improved clinical outcomes despite an increasingly high risk patient population. (19;20) In addition, public policy research has led to standardization of many aspects of the care of the cardiac surgery patient ranging from patient selection to post-operative care protocols. (21;22) Concurrently, percutaneous coronary intervention with balloon angioplasty and stenting have dramatically altered the nature of coronary surgery patients. These percutaneous therapies have been broadly applied to patients generally with less complex and proximal coronary disease, causing a decline in the overall number of coronary surgery procedures and a significant increase in the anatomic complexity and presence of comorbid illness in current patients. While recent data suggests that newer techniques such as percutaneously implanted drug-eluting coronary stents may be less effective than expected(23;24), the vigorous debate regarding the best method of revascularization (percutaneous versus surgery) has been reinvigorated. (25)

Unanswered questions
The ultimate goal of coronary bypass surgery is to improve overall survival and freedom from repeat clinical events such as angina recurrence or myocardial infarction. In this context, significant questions remain regarding methods to decrease the morbidity of the surgery in the perioperative period and to improve the long-term freedom from graft failure and disease recurrence: 1. What role does off-pump coronary bypass surgery play in further reducing coronary bypass surgery morbidity? 2. Can the technical aspects of coronary surgery be improved with image guidance to prevent early graft failures? 3. What are the optimal bypass graft materials? 4. How do the characteristics of the patient and the diseased coronary vessels play in graft failure? 5. What are the optimal pharmacologic regimens to improve long-term outcomes?

With the goal of optimizing coronary artery surgery outcomes, this thesis addresses question 1 by determining surgeon preferences for off-pump surgery, questions 2, 3, and 4 are addressed in detail using multiple prospective studies, and question 5 will be the subject of future investigations.

In contemporary clinical practice, the early to mid-term mortality and clinical event rates after coronary bypass surgery are extremely low. Recent longitudinal studies have shown survival after coronary bypass surgery to be >95%, 85-90%, and 70-80% at 1, 5, and 10 years post-operatively. (26-29) Since the expected event rate is low within the first five years after operation, studies aiming to improve the results of CABG surgery either require very large sample sizes or very long (i.e. ten-year) follow-up to be adequately powered to detect differences in meaningful clinical endpoints. In order to facilitate the feasibility of performing clinical trials in coronary bypass patients and
provide timely access to new beneficial therapies, measurement of angiographic graft 
patency of bypass surgery has been proposed as a surrogate endpoint.

1.2. Graft Patency as a surrogate marker of future clinical events

Several studies have shown that early (1-year) and mid-term (5-year) graft patency is an 
appropriate surrogate marker for future clinical cardiac events.

The Post-CABG Investigation was a two armed multicenter randomized clinical trial 
which in one arm compared the effects of aggressive lowering of low-density 
lipoprotein cholesterol (LDL-C) level (goal 1.6-2.2 mmol/L) to moderate lowering of 
LDL-C level (goal 3.4-3.6 mmol/L) on the angiographic progression of atherosclerosis 
in saphenous vein grafts. (30) The second arm of the study compared low-dose 
anticoagulation with warfarin to placebo for the same angiographic outcomes. (31) The 
primary results showed a benefit in terms of graft patency at one year in the high 
intensity cholesterol reduction group over the low intensity group but not in the 
warfarin group over placebo.

In a subsequent follow-up paper, the study authors sought to determine if graft disease 
could predict the occurrence of future clinical events. (32) A total of 1351 men and 
women who had at least one saphenous vein graft placed were enrolled. All patients 
had baseline angiograms that were centrally read. This follow-up was undertaken to 
ascertain whether asymptomatic patients who had substantial atherosclerosis
progression in at least one vein graft at baseline angiography were at a higher risk for subsequent coronary events than patients who did not have substantial atherosclerosis progression. Subsequent coronary events included death, myocardial infarction (MI), stroke, and repeat revascularization. The principle finding of the study was that in asymptomatic patients, presence of significant graft disease identified at angiography was the most important risk factor for future cardiovascular death or myocardial infarction with a hazard ratio of 2.1 (95% confidence interval 1.4 to 3.2).

The Cholesterol Lowering Atherosclerosis Study (CLAS) randomized 162 non-smoking, 40- to 59-year-old men with previous coronary artery bypass graft surgery to colestipol/niacin plus diet or placebo plus diet. Patients underwent protocol driven graft and native vessel angiography at two years after surgery. The active treatment group was found to have a less disease progression at two years. Annual clinical follow-up was performed for a further 7 years. Clinical coronary events defined as need for revascularization, nonfatal acute myocardial infarction, and coronary death) were prospectively followed. The formation of at least one new lesion found on 2-year angiography was related to the risk of any coronary event (RR=2.0; P=.03), and this risk was associated only with new lesions in the bypass grafts (RR=2.3; P=.02) and not in the native arteries.

In a single centre cohort study, Halabi and colleagues sought to determine long-term effects of early saphenous vein failure on major clinical events using the Duke Cardiovascular Databank. They examined baseline clinical and angiographic
characteristics and clinical outcomes among patients who underwent catheterization for symptom recurrence 1 to 18 months after their first CABG between 1986 to 2004. Patients were classified on the basis of their worst saphenous vein stenosis as disease-free (<25%), noncritical (25% to 74%), critical (75% to 99%), or occlusive (100%). The primary outcome measure was the composite of death, myocardial infarction, or repeat revascularization. Of 1,243 patients included in the analysis, 27.9% had no, 11.9% had noncritical, 20.8% had critical, and 39.3% had occlusive SVG disease. At 10 years, the corresponding adjusted composite event rates were 41.2%, 56.2%, 81.2%, and 67.1%, respectively (p <0.0001). On multivariate analysis, critical, nonocclusive SVG disease was the strongest predictor of the composite outcome (hazard ratio 2.36, 95% confidence interval 2.00 to 2.79, p <0.0001).

Fitzgibbon and colleagues evaluated a large single-center cohort of patients investigated during a 25-year span that included 5,065 (98% of surviving) grafts early, 3,993 grafts at 1 year and 1,978 grafts at 5 years after operation; other examinations were also performed up to 22.5 years after operation, and 353 grafts were examined after 15 years. (35-38) One and five year angiography was predominantly performed on a prospective basis on asymptomatic patients. Grafts were graded for patency and disease and the status of all patients was known at the study's end. Their study showed a relation between graft occlusion occurring >1 year after CABG and subsequent reoperation and mortality. After adjustment for baseline factors, patients with critical SVG disease at index angiography had the highest 10-year event rate (81.2%), followed
by those with occlusive (67.1%), noncritical (56.2%), and no (41.2%) SVG disease (p <0.0001).

Lytle and colleagues in a single institution retrospective analysis studied 723 patients who underwent a postoperative angiographic study that documented a stenosis of 20% to 99% in at least one saphenous vein graft and who did not undergo reoperation or percutaneous transluminal coronary angioplasty within 1 year after that catheterization. (39) For comparison, a group of 573 patients who underwent a postoperative catheterization that did not show any vein graft stenosis were also followed up. Their mean follow-up interval was 83 months. Cox regression analyses were used to identify predictors of late survival, reoperation-free survival, and event-free survival. For the entire group of patients with stenotic vein grafts, moderate or severe impairment of left ventricular function (p < 0.001), interval between operation and catheterization (p < 0.001), older age (p = 0.001), triple-vessel or left main coronary artery disease (p = 0.004), and stenosis of the vein graft to the left anterior descending coronary artery (p = 0.09) were associated with decreased late survival. A stenotic vein graft to the left anterior descending artery was a strong predictor of decreased survival (p < 0.001) and decreased event-free survival (p < 0.001). Patients with > 50% stenosis of vein grafts to the left anterior descending artery had survival of 70% and 50% at 2 and 5 years after catheterization, compared with 97% and 80% for those with greater than or equal to 50% stenosis of the native left anterior descending artery (p = 0.002)

One clinical trial that did not have routine angiographic follow-up has questioned the role of graft failure in late survival.(40) The Bypass versus Angioplasty
Investigation (BARI) was a randomized trial comparing clinical outcomes after coronary bypass surgery and angioplasty that found that in patients who had recurrence of angina symptoms after revascularization and underwent coronary angiography, progression of disease in territories that were not revascularized at the index procedure were more likely to be the cause of recurrent symptoms than graft failure. This relationship was observed in both the surgical and angioplasty groups, although the effect was significantly greater in the angioplasty group. An important limitation of this study is related to its entry criteria in which patients were to be randomized to bypass surgery or angioplasty and thus had anatomy that was suitable for angioplasty. This generally meant that the randomized patients had more proximal native coronary artery lesions and, presumably, a greater proportion of grafts were anastomosed to more proximal targets than is routinely done in clinical practice. This may lead to longer native segments distal to the graft-coronary anastomosis and result in a greater chance of symptomatic native vessel disease progression.

Similar results were seen in the CABADAS study, a clinical trial designed to compare the efficacy of low dose aspirin alone or in combination with dipyridamole and oral anticoagulants to prevent cardiac death, MI or vein graft failure after CABG. In their study, graft occlusion at 1-year was not identified as a risk factor for MI and death but was associated with angina recurrence. However, there were too few deaths (13/912 patients) in the short, one-year follow-up period, to reliably study this endpoint. Also, the myocardial infarction endpoint included perioperative myocardial infarctions which occur for a variety of reasons including insufficient myocardial protection. Further,
coronary angiography was not performed in 31% of patients with MI, as compared with 12% of patients without MI, indicating potential ascertainment bias.

In summary, the majority of clinical evidence available supports the determination of graft patency by angiography as an appropriate marker for future clinical events including mortality and myocardial infarction. Strategies aimed at improving early to mid-term graft patency are likely to be associated with improved long-term clinical outcomes.

1.3. Graft Patency: The Role of Early Technical Failure

Technical failure in the off-pump era of coronary surgery

Despite the highly favourable outcomes of CABG, a clinically significant number of patients experience early graft failure that is related to technical complications at the anastomosis site. With the rapid progress of multiple vessel angioplasty and stenting, patients referred for coronary surgery in the current era typically have diffuse calcific disease with smaller distal target vessels (<2 mm) that are significantly more difficult to sew. Technical concerns are especially relevant as more technically demanding coronary bypass procedures including off-pump surgery and use of multiple arterial grafting have gained popularity in response to the advance of percutaneous therapies.
Off-pump coronary surgery has become more popular over the past 10 years as an effort to reduce the morbidity associated with cardiopulmonary bypass. Potential advantages of off-pump surgery include decreased neurocognitive and renal dysfunction, less systemic inflammatory response, less blood transfusion and shorter hospital stays. In 2003, off pump surgery accounted for 20-30% of coronary bypass surgery in the world. However, a high-impact and provocative single centre clinical trial by Khan and colleagues in 2004 suggested that the patency rate of off-pump surgery was 10% poorer than on-pump surgery. Puskas and colleagues subsequently showed in a very well designed single centre clinical trial that there was no impairment in graft patency between the two techniques. The disparate results of these trials highlight the significant surgeon-specific variation observed in graft patency in OPCAB patients and have reinforced the need to develop a reliable method of graft patency assessment. Differences in graft patency have been ascribed to increased technical difficulty sewing a beating heart anastomosis. In conventional on pump surgery, the heart is fully arrested during the operation and the systemic circulation is supported by the cardiopulmonary bypass circuit. With off-pump surgery, the heart is kept beating and the vessel on which the graft is being sewn is stabilized with a variety of mechanical retractors. Since there is often significant residual motion and/or back bleeding at the operating site during off-pump surgery, there is concern that a beating heart anastomosis is less technically precise than an on-pump anastomosis.
Minimally invasive coronary bypass procedures have been proposed to further reduce the morbidity of the sternotomy incision and are performed through small thoracotomy incisions or even port access using thoracoscopic or robotic telemanipulation. A randomized clinical trial comparing stenting of the LAD to a LIMA to LAD bypass via a limited left anterior thoracotomy showed 16% of bypass patients had anastomotic stenosis greater than 50% at 6-month angiography. (55) Minimally invasive procedures have occasionally been associated with bypass of the incorrect coronary vessel due to poor exposure. (56) Recent angiographic follow-up studies of robotically-assisted anastomoses and automatic anastomosis connecters have also shown increased early graft failure at the anastomotic site. (57-60)

*Mechanisms of technical failure*

Technical errors in coronary bypass surgery occur due to several mechanisms. Sutures placed too deep into the target vessel at the distal portion (toe) of the anastomosis may cause total or near total occlusion at the outflow but will allow retrograde flow into the proximal native vessel. Sutures placed too deep at the proximal portion (heel) of the anastomosis may narrow the anastomosis but still allow flow into the distal target vessel. Sutures placed too deep along the sides of the anastomosis can cause narrowing or even total obstruction if they crossover to the opposite wall of the native vessel. Excessive tightening of the suture line can lead to a circumferential narrowing of the anastomosis, known as purse-stringing. Inappropriate angulation of the conduit at either the proximal or distal anastomoses may cause kinking of the graft causing flow
limitation. The entire graft (either free or in-situ) may become twisted leading to partial or total occlusion. Localized trauma to the target coronary vessel may cause endothelial disruption and subsequent thrombosis or dissection with stenosis or occlusion caused by the intimal disruption.

**Incidence of technical failure**

Published series report that 1-2% of patients have an occluded left-internal mammary (LIMA) and 3-8% of patients have greater than 50% LIMA stenosis in the immediate (<1 week) post-operative period. (61-64) Immediate postoperative saphenous vein graft occlusion has been shown in many clinical studies to occur in 2-11% of grafts with a further 10% of vein grafts having greater than 50% stenosis. (47;48;65-69) (See Table 1.1. for details) According to Fitzgibbon, the majority of these angiographic stenoses are a direct result of technical problems at the distal anastomosis. (38)

**Clinical consequences of technical failure**

The consequences of early graft failure are not benign. In situations where sutures are placed too deep or the native vessel endothelium is disrupted, the native vessel that was diseased but still had antegrade flow may become occluded, causing worse flow into the distal arterial bed after surgery. Fabricius et al. reported that in 131 patients undergoing postoperative angiography for perioperative myocardial ischemia, more
than half had significant technical problems with a graft leading to early reoperation. (70) Total 30-day mortality was 9.3% in these patients. An earlier report by FitzGibbon showed that among patients experiencing perioperative myocardial infarction by enzymatic or ECG criteria, 78% had a graft lesion that was identified by routine post-operative angiography. (71) The longer term consequences of non-occlusive stenoses caused by technical error are also significant. Fitzgibbon reported that among grafts with an immediate postoperative stenosis greater than 50%, one quarter were totally occluded at one year angiography. (72)

_Graft Assessment Technologies_

In contrast to coronary stenting, where immediate technical results are verified by completion angiogram, or cardiac valve surgery, where immediate technical results are verified by completion transesophageal echo, there is no current standard of care regarding graft evaluation in coronary surgery. Surgeons typically rely on the absence of hemodynamic compromise, and pathologic ECG changes as methods for determining the adequacy of their anastomoses. Several types of intraoperative imaging to assess graft patency in the operating room are currently available. These include methods which create an anatomic depiction of the graft and anastomosis, such as thermal angiography and contrast dye x-ray angiography; methods which attempt to quantify graft flow and flow pattern, including transit-time ultrasound, Doppler ultrasound and electromagnetic flowmetry; methods which provide anatomic characterization and flow parameters, such as high frequency duplex ultrasound,
indirect graft assessment methods including trans-esophageal echocardiography, and non-image based techniques such as probe patency. A summary of intraoperative graft patency assessment outcomes is provided in Table 1.2.

**Flow-Based Methods of Graft Assessment:**

*Ultrasound / Doppler flowmetry:* Ultrasound waves are pulsating pressure waves above the audible range. Doppler measurement of blood flow employs the Doppler effect on an ultrasound beam to calculate volumetric rate of flow. The Doppler effect occurs due to an apparent change in the frequency of an ultrasound wave reflecting off of a moving object. It is thought to be due to the relative motion between the reflector and transducer and there is an increase in frequency if the movement is toward the transducer and a decrease in frequency if the movement is away from the transducer. Typical pulse-wave Doppler probes contain one piezoelectric element which functions as the transmitter and receiver of ultrasound waves and the measurement occurs at a specific depth. Since the quantity actually being measured is the velocity of flowing blood, conversion to a volumetric rate of flow is highly dependent on the diameter of the vessel and the angle of insonation of the ultrasound beam. The vessel diameter must be entered manually by the user based on B-mode ultrasound scanning or derived from a multi-gated ultrasonic beam. Error created by diameter estimation is significantly magnified since flow is a function of the square of the vessel radius. (73) When studied in off-pump coronary bypass patients, Doppler flowmetry showed poor
sensitivity for detecting hemodynamically significant (>50%) stenoses and even total occlusions. (74;75)

Recent advances in high frequency ultrasound transducers and increased computing power have led to new compact sterilizable ultrasound probes that provide both Doppler flow data and very detailed B-mode anatomic information that may potentially have higher resolution than any current imaging technique. (76-78) In a study by Budde and colleagues, several anastomoses were constructed on animal and cadaveric models with specific technical errors present. (79) The grafts were then studied with high frequency epicardial ultrasound, selective contrast dye x-ray angiography, angioscopy and pathologic analysis with latex casts to determine the efficacy of the high frequency ultrasound technique to detect these errors. Using pathologic analysis as the reference standard, the authors found that the high frequency ultrasound technique had 98% sensitivity and 100% specificity, versus angiography which had a sensitivity of 75% and a specificity of 81%. Potential limitations of extrapolating these results to the operating room setting include difficulty achieving the same quality of images on the beating heart. One advantage of this technique over other intraoperative imaging technologies is that the ultrasound probe can also be used to find intramyocardial coronary vessels and potentially even image the target vessel to find an optimal anastomosis location. The results of ongoing clinical studies in the operating room will determine the role of this technology in the future.
**Electromagnetic Flowmetry:** Electromagnetic flowmetry is a technique of flow measurement that was used prior to the introduction of more user friendly Doppler-based techniques. This technique estimates blood flow by measuring the induced electromotive force created when flowing blood (an electrolyte) is exposed at a right angle to a magnetic field. Electrodes measure the induced voltage which is a function of the magnetic field and the blood flow in the vessel. Accurate measurements require precalibration, constant zeroing, segmental exposure of the vessel wall, and a range of sterilized probes of varying diameters to ensure a close fit around the vessel wall. In situations where the vessel wall is not of uniform thickness, the flow signal may be less accurate as the distribution of charged particles is not uniform within the vessel lumen. The technique is also sensitive to patient’s hematocrit. This method has not been widely used due to these substantial limitations. (80;81)

**Transit Time Ultrasound Flow (TTF):** TTF is a simple flow measurement technique used commonly in off-pump coronary surgery which provides detailed graft flow characteristics. Transit-time ultrasound flow uses ultrasound technology but does not employ the Doppler effect. In TTF, 2 small piezoelectric crystals (upstream and downstream) transmit ultrasound waves to a reflector on the opposite side of the vessel. The distance and angle between these three components is constant. The time required for the ultrasound wave to travel from the upstream crystal to the downstream crystal via the reflector and the time required for the ultrasound wave to travel from the downstream crystal to the upstream crystal via the reflector are recorded. The ultrasound wave will travel faster when going in the direction of flow meaning that the
upstream and downstream travel times, known as transit times, will be different. The flow rate is directly derived from the time difference, where a larger time difference means faster flow. (See Figure 1.1.) Since the beam of the ultrasound is a larger diameter than the vessel lumen, measurement of the vessel diameter is not necessary. Thus, this method derives a flow rate that is independent of vessel diameter, vessel shape, probe angle, or blood flow characteristics.

TTF provides measurements of mean volumetric flow, visualization of systolic and diastolic flow pattern, and pulsatility index. Mean volumetric flow rate is the total flow per minute measured as a velocity by the flow probe and converted to a volumetric flow rate by multiplication of the cross-sectional area of the vessel (See Figure 1.1.). The mean flow can be influenced by several factors including flow limiting stenoses in the graft, flow competition from the native vessel, and stenoses at the proximal or distal anastomoses. In addition, the perfusion pressure and resistance in the outflow arterial bed influence graft flow according to Ohm’s Law:

\[ \text{Flow} \ (Q) = \frac{\Delta P}{R} \]

where:
- \( Q \) = flow
- \( \Delta P \) = perfusion pressure difference
- \( R \) = resistance in vascular bed

Vessel diameter, the length of the conduit, and the blood viscosity influence resistance and thereby flow according to Poiseulle’s Law:

\[ \text{Flow} \ (Q) = \frac{\pi r^4 \Delta P}{8 \eta L} \]

where:
- \( Q \) = flow
- \( r \) = vessel radius
- \( \Delta P \) = perfusion pressure difference
- \( \eta \) = dynamic fluid viscosity
- \( L \) = graft length
The pulsatility index is a quantity obtained by dividing the difference between maximal and minimal flow by the mean flow. (82)

The flow pattern is determined by referencing the flow tracing to the coupled ECG tracing. In the normal coronary circulation, after a short systolic peak flow, the majority of coronary blood flow occurs in diastole. (83) Similar flow patterns are expected in patent grafts. (84) In the right coronary artery, there is less diastolic predominance in the flow pattern. (83) In addition to visual assessment of flow pattern, flow may also be quantified according to the percent of graft flow occurring in diastole. Visual assessment of flow waveforms has been shown to be unreliable. In a survey conducted by Jaber and colleagues, international experts in the field of cardiothoracic surgery were provided TTF waveforms of normal and stenotic grafts verified by x-ray angiography. (85) Among the 19 responding surgeons, 24% would have erroneously revised at least one fully patent anastomosis, 58% would have accepted at least one anastomosis with moderate stenosis, and 72% would have accepted at least one anastomoses with severe stenosis. The authors concluded that visual assessment of the waveform was insufficient to detect significant anastomotic errors.

TTF has gained popularity among surgeons performing off-pump surgery. Although the technique appears to identify occluded grafts, there is no general agreement as to what parameters distinguish between moderately stenotic and patent grafts. (86) Several studies have analyzed the ability of these variables to predict graft problems in
comparison to postoperative contrast dye x-ray angiography. (87-91) The most commonly accepted criteria are from D’Ancona, where revision is recommended for grafts with a pulsatility index > 5, mean flow less than 10-20cc/min or a predominantly systolic flow pattern (>50% of flow in systole). (92) Fast Fourier transform spectral analysis has been proposed as a superior method of graft assessment, but this is also not validated beyond small empirical studies. (93) The Fast Fourier algorithm uses the amplitude and phase characteristics of the waveform to identify waveform characteristics that are not seen in the usual time domain waveform.

D’Ancona has also suggested that formal functional tests of graft flow may aid in patency decisions. (84) These include measuring mean flow with the proximal native vessel occluded by a snare suture and also with the distal native vessel snared. These manoeuvres, applicable only to off-pump surgery, allow for isolation of the proximal and distal portions of the anastomosis to be tested, although they do increase the potential risk of damage to the native vessel. Functional testing may also be performed on the beating heart patient with a dobutamine infusion to increase the myocardial oxygen demand. Since oxygen delivery to the heart muscle is flow dependent, there should be an accompanying increase in graft flow.

**Anatomic Methods of Graft Assessment:**

*Thermal Angiography:* This technique requires a temperature difference between the graft or coronary artery and the myocardium. This is usually achieved by injecting cold
or warm cardioplegia, which will change the temperature of the graft or native vessel prior to changing the temperature of the myocardium. Another technique is to unclamp in situ grafts and allow warm systemic blood to perfuse the grafts. The differences in heat signatures from warm and cold tissues are captured by an infra-red camera and a visible image is produced, although the spatial resolution of the image is generally poor. Although not widely accepted, this technique is used clinically by some groups. (94-96) Recent improvements in technology have yielded better images, but no objective evaluation or validation versus x-ray angiography or transit-time flow has been performed. (97)

**Contrast Dye X-Ray Angiography:** Contrast-dye x-ray angiography is regarded as the ‘gold-standard’ for patency assessment. Conventional contrast x-ray angiography can be performed in the cardiology catheterization lab soon after surgery or in “hybrid operating rooms” which are fully functional operating rooms and have state-of-the-art angiography equipment. (73) Few hospitals currently have such operating rooms, and it is not currently practical to schedule every open-heart patient in such a room. With the increasing use of stent-grafting to treat diseases of the thoracic aorta, the number of hybrid operating rooms is dramatically expanding. Techniques to perform intraoperative contrast x-ray angiography of bypass graft using movable floor or ceiling mounted or portable fluoroscopy equipment have been described with intra-arterial access obtained through either the radial artery or femoral artery. The technical quality of these images has generally been substandard for several technical reasons including lower quality x-ray equipment, use of non-x-ray compatible operating room tables.
causing significant artefact, and operator inexperience. Angiography performed postoperatively in the catheterization lab does not allow for graft revision. Intravenous contrast dye has known nephrotoxic characteristics which may be exacerbated in the perioperative period as cardiopulmonary bypass is associated with renal dysfunction.(98) Additionally, due to the large dose (typically 30,000U) of intravenous heparin given for coronary surgery, percutaneous cannulation of the femoral artery with a 6F catheter for graft angiography may pose greater risks for perioperative bleeding from the puncture site and local hematoma. There is also potentially increased risk for disruption of the aortic cannulation site and graft proximal anastomoses with advancement of the catheter for selective angiography. Since these procedures are time consuming, invasive, and cumbersome, they have not been accepted into general practice.

**Angioscopy and Intravascular Ultrasound:** Angioscopic graft evaluation involves indirect visualization using a fiberoptic camera passed within the lumen of the graft. This allows visualization of the graft and anastomosis on a monitor in real time. Authors have described its clinical use in detecting graft or native vessel thrombosis and in the case of in-situ peripheral bypass, the presence of venous valves.(99-105)

The technique is limited by camera size and the camera is usually too large to assess the distal circulation. Also, to achieve a visual field clear of blood, often several litres of saline irrigation are required that can cause volume overload and hemodilution.(106)
The utilization of this technique in assessing coronary surgery results has been very limited although it is sometimes used in infra-inguinal bypass surgery.

Intravascular ultrasound (IVUS) is a method of vessel imaging in which a high frequency ultrasound transducer is attached to the tip of a coronary catheter and high resolution ultrasonic images of the vessel lumen and wall are visualized in real time. The general technique of IVUS is similar to selective x-ray angiography and it may be used as an adjunct to angiography. IVUS requires femoral or radial artery access as well as fluoroscopy equipment to guide the catheter. Although the technique is extremely expensive due to the cost of disposable catheters and requires significantly more time than other patency assessment methods, it is the most sensitive technique to determine any anatomic problems in bypass grafts.(107-109) Due to concerns about cost, high level of technical expertise required to perform the study and the potential to disrupt fresh anastomoses which need to be crossed by the catheter, there is very limited experience with this technique in the operating room.(109)

*Fluorescent-dye angiography:* A recent innovation in intraoperative graft assessment has been fluorescent dye angiography.(110) This technique employs a fluorescent dye (indocyanine green) which is injected into the vessel of interest. The graft is simultaneously illuminated with a near infra-red laser light which excites the dye causing fluorescence in the near-infra-red range. Although the dye fluorescence is not visible to the human eye, the signal can be converted into a digital image on a computer
screen that can be viewed in real time. Preliminary ‘first-in-human’ investigations with the device show that high quality images are possible which may identify intraoperative graft problems.(110) The development and validation of this technology will be described in more detail in Chapters 3 and 4.

**Indirect Graft Assessment Techniques:**

*Transesophageal echocardiography:*

Indirect assessment of coronary graft patency can be performed using transesophageal echocardiography (TEE), where wall motion abnormalities may represent graft problems. Since the routine use of TEE is increasing in cardiac surgery, this modality is gaining increasing importance in graft assessment.(111-113) A recent study suggests that up to 17% of intraoperative clinical interventions may be initiated by information obtained from TEE, including fluid administration or anti-ischemic therapy. (114) In one of the 75 patients examined by TEE in this study, new wall motion abnormalities after chest closure led to discovery of a kinked bypass graft. Inability to visualize graft flow or graft anatomy limits the ability to discern the cause of new wall motion abnormalities which may be due to graft failure or poor regional myocardial protection.

**Non-Imaging Based Techniques:**

*Probe Patency:*
A common approach to graft assessment in the operating room is to pass a small 1-2 mm probe into the heel (proximal end) or toe (distal end) of the coronary anastomosis while it is being sewn. This technique is potentially hazardous since it may cause intimal disruption in the native coronary vessel. Also, probing the distal anastomosis after the toe stitches have been placed does not ensure patency since a deeply placed stitch through the posterior wall of the native coronary will not always cause occlusion until the anastomosis has been fully tightened and tied down. Also, occlusive stitches may be placed after the probe has been removed and the anastomosis may be overly-tightened (purse-stringed) causing significant stenosis or occlusion. While probing anastomoses is a common practice, no studies validating this technique have been performed.

**Summary of Intraoperative Graft Assessment**

Technical concerns are highly relevant in the current era as more technically demanding coronary bypass procedures including off-pump surgery and multiple arterial grafting have gained popularity in order to decrease the morbidity and increase the longevity of the operation. Given that early graft failures are more common than appreciated by many surgeons and may cause significant perioperative and long-term morbidity, lack of a well validated and routinely used form of intraoperative graft assessment represents a significant opportunity to improve coronary artery bypass surgery outcomes.
1.4. **Graft Patency: The Role of Conduit Selection**

**Saphenous Vein Grafts and the problem of early attrition:**

The technique of coronary bypass surgery using saphenous vein graft conduits was first pioneered by Favaloro in 1967 and gained rapid adoption due to ease of conduit harvest and ease of anastomosis construction due to the large diameter and thickness of the vessel wall. (115) Their potential length allows them to access every vessel on the heart. Until the mid 1980s, coronary bypass surgery with only saphenous vein conduits was the standard method of coronary revascularization. Local complications of saphenous vein harvest include wound infection, hematoma, and skin necrosis, and wound dehiscence.

In the late 1970s and 1980s, several groups noticed high rates of early vein graft attrition and this did not appear to occur in left internal thoracic artery conduits. (116-119) Serial angiographic studies have shown that 10-25% of SVGs are occluded by one year following surgery. Intimal hyperplasia develops in nearly all saphenous vein bypass grafts within 6 weeks after exposure to arterial blood pressure. (120;121) The cellular events that account for this intimal response include migration and proliferation of vascular smooth muscle cells followed by extracellular matrix synthesis and deposition. (120)
Arterialized vein grafts are susceptible to intimal hyperplasia and atherosclerosis for several reasons. Explanted vein grafts develop vessel wall ischemia due to a loss of a functional nutrient-supplying vasa. (122) Arterialized vein grafts are also subject to a significant increase in wall stress. (123) Ischemia and wall stress induce endothelial dysfunction or loss, which reduces the availability of endothelial factors that prevent inflammatory cell adhesion, thrombosis, and smooth muscle cell proliferation, including chiefly prostacyclin, adenosine, and nitric oxide. (123;124)

**Patency Outcomes of Saphenous Vein Grafts**

Many studies have investigated saphenous vein graft failure rates in the early (1-year), mid-term (3-5 year) and late (>5 year) periods. Table 1.1 summarizes a large number of patency studies ranging from the early days of coronary bypass grafting into the current era. In general these studies have been performed as serial cohort follow-up studies on either symptomatic or asymptomatic patients, or as part of randomized clinical trials with pre-specified graft patency outcomes. Overall, the rate of saphenous vein graft occlusion at one year is 10-25%. After the first year, vein grafts show a fairly linear rate of attrition with an annualized rate of occlusion of approximately 1-2%/year. The five year vein graft patency is generally 70-80% and this decreases to 60% by 10 years of follow-up. (See Table 1.1. for a summary of patency studies)

**Predictors of Vein Graft Failure**
Several angiographic studies have examined the causes of vein graft failure. The Post-CABG study found that more aggressive lipid lowering was effective in preventing progression of atherosclerosis in SVGs but warfarin had no effect.\(^{(125)}\) Using variables measured at baseline, independent prognostic factors for atherosclerosis progression in SVGs included: decreasing maximum stenosis of the target vessel at baseline angiography\(p<0.001\), increasing years post-CABG surgery\(p<0.001\), randomization to the moderate lipid lowering strategy\(p<0.001\), prior myocardial infarction\(p<0.001\), high triglyceride level\(p<0.001\), small minimum graft diameter\(p<0.01\), low HDL cholesterol\(p<0.01\), high LDL cholesterol\(p<0.01\), high mean arterial pressure\(p<0.05\), lower ejection fraction\(p<0.05\), male gender\(p<0.05\); and current smoking\(p<0.05\).\(^{(126)}\)

Goldman and colleagues have prospectively studied a large cohort of CABG patients involved in Veteran’s Affairs Cooperative Studies assessing various anti-platelet regimes with serial angiography.\(^{(127-130)}\) They found that in 257 patients with 634 vein grafts at three years after surgery, predictors of vein graft occlusion included vein preservation in the operating room at temperature greater than \(5^\circ\text{C}\) \(p=0.004\), higher serum cholesterol \(p=0.02\), smaller diameter of recipient artery, \(p=0.03\) and greater number of proximal anastomoses \(p=0.03\). \(^{(128)}\)

Shah and colleagues in Australia have extensively followed a large cohort of patients with CABG who have had follow-up angiography predominantly for symptom recurrence.\(^{(131)}\) Over a 15 year period, 2266 (61\%) vein grafts were patent, and 1449
(39%) were occluded. The risk factors for graft occlusion included a younger age (p<0.001), ejection fraction<30% (p=0.047), small coronary artery diameter (p<0.001), large conduit diameter (p<0.001), and the coronary artery grafted with highest rate of graft occlusion in the right coronary artery and least in the left anterior descending artery territory (p=0.002). Longer interval from operation to repeat angiogram was also associated with graft occlusion.

**Strategies to Improve Vein Graft Patency**

Many attempts have been made to slow the progression of saphenous vein graft disease including pharmacologic and gene-therapy based approaches. Technical considerations such as use of off-pump surgery were discussed previously in this chapter. During the 1980s, several clinical trials examined the role of antiplatelet medications, primarily aspirin, in the pre-operative, early and late post-operative periods. Preoperative aspirin did not improve graft patency but increased perioperative bleeding. A meta-analysis of aspirin in the early post-operative period by Fremes and colleagues showed a 40% reduction in early graft occlusion.(132) In series by Goldman and colleagues, aspirin use prevented early graft occlusion but had no effect on late graft occlusion.(127;130) Aggressive risk factor lipid lowering therapy and smoking cessation have been shown to slow the progression of vein graft atherosclerosis. (133) Novel attempts at using gene-therapy with the oligonucleotide edifoligide, a competitive inhibitor of E2F, a transcription factor that helps promote smooth-muscle cell proliferation have been shown to be ineffective versus placebo.(134) A recent study suggests that an
atraumatic technique of harvesting saphenous vein grafts with their surrounding tissues may yield improved patency. (135-137)

**Arterial conduits for Bypass Surgery**

Arterial grafts have been considered for constructing bypass grafts since Kosselov used the LITA in 1961 (14) but were quickly supplanted by saphenous vein grafts due to the relative ease of vein harvesting. (17) This trend continued until reports by Grondin, Loop and others showed both poorer early to mid-term patency and poorer mid-term survival for vein grafts versus the left ITA grafted to the left anterior descending (LAD) coronary artery. (138-140) With increased experience in harvesting technique, the left ITA use has become the current standard of care and used routinely to bypass the LAD. The superior patency of the left ITA has prompted increased interest in using the right internal thoracic artery as well as other arterial conduits for coronary bypass. These included the internal thoracic artery, the right gastroepiploic artery, the inferior epigastric artery and the radial artery. The ideal coronary bypass conduit is easy to harvest, has few complications at the donor site, has adequate length to reach all coronary territories, is easy to handle, has consistent diameter that approximates the size of the target vessel and has a low propensity for spasm. The right gastroepiploic and inferior epigastric arteries have largely been abandoned.

*Arterial Graft Spasm and Pharmacology*
Arterial grafts are generally more difficult to harvest and more prone to injury than saphenous vein grafts. A significant concern with all arterial grafts is spasm, where segments of the conduit become focally narrowed in response to various stimuli. The different arterial conduits have differential contractile responses to a variety of stimuli.(16) Potential causes of early graft spasm include mechanical stimulation from surgical trauma, locally released vasoconstrictors, neural factors, circulating hormones, and exogenous vasoconstrictors and inotropes. In in-vitro isolated organ bath studies, cross-sectioned rings of bypass grafts mounted on wires have been exposed to various mechanical and pharmacological stresses.

To examine the relative contractile strength, two vasoconstrictor agents have been studied extensively: potassium(K⁺) ions and norepinephrine.(141;142) K⁺ causes a receptor-independent vasoconstriction by hyperpolarizing K⁺ channels on smooth muscle, allowing the voltage-operated Ca²⁺ channels to open and intracellular Ca²⁺ to rise, resulting in contraction. Norepinephrine causes contraction by both depolarization of the tissue through voltage-operated Ca²⁺ channels and also by calcium release from intracellular sources.

The contractile response to K⁺ in radial arteries is significantly stronger than in ITA or gastroepiploic arteries.(143) Other potential spasmogens for blood vessels, are (1) endothelium derived contracting factors such as endothelin; (2) prostaglandins such as thromboxane A 2 (TxA2) and prostaglandin F2α (PGF2α); (3) platelet-derived contracting substances such as 5-hydroxytryptamine (5-HT) and TxA2; (4) substances
released from mast cells and basophils such as histamine; (5) muscarinic receptor agonists such as acetylcholine; and, (6) renin-angiotensin system related substances such as angiotensin II. (144-152) In in-vitro studies, He and colleagues found that endothelin-1, prostanoid receptor agonists Thromboxane A2 and PGF2α, and α-adrenoceptor agonists are the most important vasoconstrictors in the human ITA. (153) The radial artery is more reactive than the IMA to constrictive stimuli from angiotensin II, endothelin-1, serotonin, and thromboxane A2. (154) Interestingly, the proximal radial artery has been shown to be more reactive to contractile stress than the distal portion. (155) but for ITA grafts, the distal end at the bifurcation is more contractile. (156) The endothelium also plays a significant role in vascular tone. Studies of endothelial function have shown that arterial bypass graft endothelium can produce more vasorelaxant nitric oxide (NO) than venous endothelium, with maximal NO production by the ITA. (148;157) In terms of vasorelaxation, the radial artery, GEA, and ITA all relax equivalently to acetylcholine, an endothelium-dependent agent, and to nitrates, which are endothelium-independent. (158;159) A functional classification of artery types was developed by He and Yang that categorizes arteries into three groups based on their reactivity profiles: (See Table 1.3): 1. somatic arteries including the ITA and IEA, 2. splanchnic arteries including the GEA and 3. limb arteries including the radial artery. (160) Types II and III are generally believed to be more spastic than Type 1. (161;162) Histological properties which contribute to the greater contractile response seen in the radial artery include increased density of myocytes in the arterial wall and thicker muscular media versus other arterial conduits. (163;164)
Pharmacologic techniques to prevent perioperative vasospasm of arterial grafts are currently evolving and several different classes of drugs have been used for this purpose including nitrates, phosphodiesterase inhibitors, calcium channel blockers and alpha-adrenergic antagonists.

**Nitrates**

Organic nitrates are effective against a range of constrictor stimuli. The mechanism of action for these vasodilators is that they release NO, a powerful stimulant for guanylate cyclase, which raises cGMP in the smooth muscle cell thereby reducing intracellular calcium and causing smooth muscle cell relaxation. Nitrates are effective in reversing virtually all causes of vascular spasm, regardless of the nature of the contraction. Although they are effective in reversing either receptor-mediated or K⁺-mediated contraction, they are more effective in blocking receptor-operated channels than blocking depolarizing agent-mediated contraction.

**Phosphodiesterase inhibitors:**

Phosphodiesterase(PDE) inhibitors also raise cGMP level in smooth muscle cells, but do so by preventing its breakdown. Papaverine is a non-specific agent that elicits a vasorelaxive effect by some PDE inhibition as well as decreased calcium influx and inhibition of the release of calcium from intracellular stores. Green introduced the use of papaverine in surgery in 1971. Papaverine has been shown
to increase the ITA diameter by up to 20% and mitigate contractile responses to alpha-adrenergic agents but may deleteriously affect endothelium-dependant relaxation.\textsuperscript{(170;171)} It is believed to be effective for 30min-five hours depending on the period of exposure to the vessel. Since papaverine is highly acidic(pH 4.4-4.8), the solution is generally buffered in Ringer’s lactate or heparinized blood. Unbuffered papaverine can be highly toxic to the endothelium.\textsuperscript{(172;173)} Other PDE inhibitors include milrinone, a positive inotrope and selective PDE-III inhibitor.

**Calcium Channel Blockers**

Calcium channel blockers reduce Ca\textsuperscript{2+} influx by blocking voltage-operated Ca\textsuperscript{2+} channels, thereby preventing the effect of depolarizing agents such as K\textsuperscript{+}. More complete vasorelaxation is achieved using dihydropyridine derivatives such as nifedipine, nicardipine and amlodipine versus diltiazem or verapamil. Calcium channel blockers are less efficacious at diminishing the contractile response to angiotensin II, endothelin-1, or thromboxane A2.\textsuperscript{(174)} Thus calcium channel blockers are not generally used as a monotherapy to prevent vasospasm but are generally used in combination with nitrates or papaverine for intraoperative prophylaxis. Oral calcium channel blockers are used frequently in postoperative patients to prevent vasospasm in radial artery grafts.

**Alpha-adrenergic antagonists**
In the perioperative period, there are elevated levels of endogenous and exogenously administered alpha adrenergic agents in the circulation which may lead to graft spasm. The radial artery in particular is susceptible to $\alpha$-adrenergic stimulation due to the high prevalence of $\alpha_1$-adrenoreceptors and the endothelial surface. The use of the nonselective $\alpha$–adrenergic receptor blocking agent phenoxybenzamine to locally treat radial artery grafts ex-vivo in the operating room was first described by Taggart and colleagues in 2000.\(^{(175)}\) While the action of phosphodiesterase inhibitors is fairly short-lived, phenoxybenzamine prevents response to $\alpha$–adrenergic stimulation in the radial artery for over 18-48 hours.\(^{(171;176-178)}\) Locker and colleagues have found similar relief of graft spasm in-vitro with phentholamine methansulphonic (regatine) although the duration of action has not yet been described.\(^{(179)}\) $\alpha$–adrenergic blockers are generally not effective at preventing spasm from vasopressin, angiotensin II, endothelin-1, and $K^+$. Given the varying ability of each individual agent to prevent graft spasm, combinations of agents are typically used.
Clinical Use of Arterial Grafts:

Left Internal Thoracic Artery

The LITA originates from the left subclavian artery and runs along the lateral border of the sternum. At the sixth intercostal space it divides into the musculophrenic artery and the superior epigastric artery. Histologically, the LITA graft is composed of intimal and subintimal layers that lie on an internal elastic lamina with few fenestrations. The muscular media layer has numerous (6 to 12) elastic lamellae.(180) It is speculated that this artery is relatively protected from intimal hyperplasia by the absence of large fenestrations which would allow smooth muscle migration leading to intimal hyperplasia.(180) Harvest of the LITA is generally performed as a pedicle with its two adjacent veins and some fatty areolar tissue. The artery may also be harvest in a skeletonized manner, where it is harvested without any surrounding tissue. Skeletonization has been speculated to increase conduit length and diameter in small case series but these benefits have been questioned by a recent prospective study.(181-184) Skeletonization does appear to result in less sternal devascularization, especially during bilateral internal thoracic artery (ITA) harvest (described later in this chapter).(181;182) The skeletonized method of harvest is more technically demanding than harvesting the artery as a pedicle and may increase the risk of injury.

Patency Studies
Although no randomized clinical trials have directly compared LITA to saphenous vein patency, a tremendous body of literature supports the superiority of the LITA in early, midterm and especially late patency. Landmark studies from the Montreal Heart Institute and the Cleveland Clinic showed superior patency of the LITA to saphenous vein grafts when grafted to the anterior descending coronary artery. Overall, arterial and vein grafts to the LAD system have higher patency due to a larger target vessel and arterial bed. Expected one, five and ten year graft patencies for the internal mammary artery are 95-98%, 90-95% and 88-90% respectively. (see Table 1.1 for details) Patency appears to be similar when the LITA is used as a sequential graft although this is technically more difficult and used infrequently by most surgeons.

The left internal thoracic artery rarely develops late atherosclerosis and the late attrition rate of ITA grafts is extremely low. In a longitudinal retrospective series of symptom-directed angiograms from the Cleveland Clinic Foundation, independent risk factors for LITA graft occlusion include the degree of proximal coronary stenosis, female sex, presence of peripheral vascular disease and smoking.

**Clinical Studies**

Subsequent studies showed dramatic short and long-term survival benefits of LITA bypasses to the anterior wall of the heart, presumably due to improved patency, and use of this graft has become the current standard of care in coronary surgery.
Loop and colleagues in their landmark cohort study found that patients receiving only vein grafts had increased relative risk for late mortality (RR 1.6).\(^{(189)}\) In a subgroup analysis of the Coronary Artery Surgery Study (CASS), after multivariable analysis, patients receiving a LITA graft had enhanced survival (RR 0.73, 95 percent confidence interval, 0.64 to 0.83).\(^{(190)}\) The survival advantage was noted in all subgroups.

**Right Internal Thoracic Artery**

Given the proven success of the LITA as a bypass conduit to the anterior circulation of the heart, many surgeons have speculated that the RITA is an ideal candidate for revascularization of non-LAD targets. The anatomy and histology of the RITA graft is virtually identical to the LITA.

The RITA can be used in several different configurations depending upon the location of the target vessel. In situ bypasses may be achieved with the RITA in three configurations: 1: the LITA is used to bypass the LAD and the in situ RITA is used to bypass the right coronary artery, 2: the RITA is used to bypass the LAD and the LITA is used to bypass either a large diagonal branch or the most important branch of the circumflex coronary artery, 3: The LITA is used to bypass the LAD and the RITA is brought out through the transverse sinus behind the heart to the branches of the circumflex coronary artery. Use of the RITA through the transverse sinus is complicated by instances of inadequate length to reach the most distal obtuse marginal branches.
The free RITA provides additional length and can be used as an aortocoronary graft, taken off a proximal graft hood or vein patch, or used in a T-graft or Y-graft configuration, usually off of the LITA. Both right coronary and circumflex coronary artery branches can be bypassed distally with the free RITA. Graft placement through the transverse sinus may subject the conduit to unrecognized tension and distortion and also obscure bleeding along the pedicle. Placement of a pedicled RITA anteriorly across the mediastinum imposes an extremely high risk of conduit injury during future reoperative surgery.

Relative contraindications to bilateral ITA grafting include severe chronic obstructive pulmonary disease where there is increased risk of sternal dehiscence, particularly in steroid-dependent patients, diabetics, and obese patients. The most dreaded complication of bilateral ITA harvest is deep sternal wound infection precipitated as a result of devascularization of the sternum. Diabetics, who comprise up to 40% of the coronary bypass surgery population, are most prone to this complication due to concomitant microvascular disease. The overall incidence of deep sternal wound infection is 0.5% in patients receiving single ITA grafting versus 1.6% in patients receiving bilateral ITA grafting. Other higher risk groups include obese patients, elderly patients and patients with chronic obstructive pulmonary disease. Decreased rates of deep sternal wound infection have been achieved when one or both ITA grafts are skeletonized. Skeletonization involves harvesting the ITA without its associated pedicle of veins, lymphatics, transverse intercostal muscle or internal
thoracic fascia. The benefit of skeletonization is attributed to less disruption of intercostal vessels and sternal branches leading to less sternal devascularization. Skeletonization also preserves intercostal nerve supply and may lead to less paresthesia in the chest wall after surgery.\(^{(181)}\) The major disadvantages of skeletonization include the additional operating time and technical expertise required for this approach. There are no large longitudinal angiographic studies examining patency of skeletonized ITA grafts but several reports indicate no significant decrement versus pedicled harvesting.\(^{(193-195)}\)

**Patency Studies**

Overall, the expected right ITA patency is between 92-96% and 90-92% at 1 and 5 years respectively.\(^{(181)}\) Patency outcomes of the right ITA are affected by both target vessel location and the severity of proximal stenosis in the target vessel. The use of the in-situ right ITA to the circumflex system through the transverse sinus was found by Rankin and colleagues to have poorer patency (75%) versus right ITA grafts across the anterior aspect of the heart, which had a patency rate of 100%.\(^{(40)}\) Others have shown excellent right ITA patency to circumflex targets.\(^{(41)}\) Right ITA grafts also have diminished patency when grafted to the right coronary territory.\(^{(42)}\) Poor patency to right-sided targets may be due to several technical factors. The right coronary artery is often severely diseased including distally into the crux and proximally placed grafts may eventually occlude due to progression of native distal disease. Alternatively, inadequate length may cause the right ITA to be placed under considerable tension causing collapse of the vessel lumen when the heart is in its final anatomic lie after
cessation of cardiopulmonary bypass. The issue of patency of free versus in-situ right ITA grafts remains controversial with the emerging evidence showing improved patency in in-situ ITA grafts.(43)

**Clinical Studies**

Lytle and colleagues at the Cleveland Clinic have rigorously studied longitudinal outcomes of BITA patients. In a recent review of twenty-year outcomes, they found survival at 7, 10, 15, and 20 years was 89% versus 87%, 81% versus 78%, 67% versus 58%, and 50% versus 37%, respectively comparing BITA patients to those with LITA and veins (p < 0.0001).(27) The most comprehensive review of the use of bilateral ITA was performed by Taggart and colleagues.(196) In their metaanalysis of 9 non-randomized studies of 15 269 patients, the 4693 patients who underwent BITA grafting had significantly better survival (RR 0.80 95% confidence interval 0.7 to 0.94) in intermediate to late follow-up. Despite the mounting evidence in support of BITA grafting, reports from the Society of Thoracic Surgeons database indicate that BITA use occurs in less than 4% of all isolated coronary bypass procedures today.(27)

**Radial Artery**

The radial artery bypass graft was first introduced by Carpentier in 1971 as a technique to mitigate early attrition seen in saphenous vein grafts.(197) In the original technique, the radial artery was harvested as a skeletonized graft and due to its propensity for
spasm, was mechanically dilated with metal probes. The initial patency results were disappointing and the use of this graft was discontinued. On the post-mortem exam of some of the original radial artery grafts, significant intimal hyperplasia and severe narrowing of the lumen was noted. (198) Acar and colleagues demonstrated that some of the radial arteries that had early graft spasm from the original series by Carpentier were patent at late repeat angiography. (199)

Given these unexpected findings, Carpentier's group in Paris reintroduced the use of the radial artery in 1989. (199) They altered the original harvest procedure by taking the radial artery as a pedicle with its accompanying veins to minimize handling the artery directly as opposed to the previous skeletonized technique. To relieve vasospasm, they intraoperatively performed slow intraluminal dilatation with papaverine, a non-specific phosphodiesterase inhibitor that is a potent vasodilator and they administered calcium channel blockers postoperatively. The early patency rate of the first 56 grafts studied within 2 weeks of operation was 100%. Six grafts showed focal narrowing, half of which improved with intra-graft vasodilator infusion. These positive findings reinvigorated the use of the radial artery as a bypass conduit.

Due to its muscular media layer, significant attention has been placed on the prevalence of: 1. radial artery spasm, which appears to occur due to mechanical stimulation at time of harvesting, and 2. diffuse graft narrowing (string sign), which occurs within the first post-operative year as an adaptation to competitive flow from the native vessel. To date, due to low event rates, no studies have been adequately powered to prospectively
demonstrate clinical benefit of calcium channel blockers (used to prevent arterial graft spasm, particularly in radial arteries) or lipid lowering therapy on arterial graft occlusion rates.

**Angiographic Studies**

In the current era, several studies have documented the early to midterm angiographic patency of the radial artery. The majority of these studies are retrospective cohort analyses of unselected patients receiving radial artery grafts. (See Table 1.1) Overall, expected radial artery patency at 1 and 5 years is generally 92-94% and 88-92%, respectively. Amano and colleagues found radial graft patency was 93% in 229 selected patients 1.5 years after surgery and diffuse narrowing was observed in 4.8% of radial grafts. (200) Khot and colleagues studied 310 symptomatic patients at a mean of 18 months after coronary bypass surgery showed distinctly poorer radial patency results (51.3%) compared with 64% for saphenous veins and 90% for ITAs. (201) This analysis has been severely criticized for flawed methodology including inclusion of a highly skewed population in which 22% of patients had redo surgeries, substantial missing data regarding clinical and angiographic characteristics and medical therapy, and, since only symptomatic patients were restudied, the true proportion of occluded radial arteries was not possible to determine. Cameron and colleagues showed in a cohort of 50 asymptomatic patients that 5 year radial artery patency was 89%. (202) Tatoulis and colleagues studied 2127 angiograms in symptomatic patients at a mean follow-up period of 76.2 months. (203) They found LITA patency of 96.4%, RITA
patency of 88.3%, radial artery patency of 89.3% and vein graft patency of approximately 60%. Possati and colleagues studied 84 radial arteries at 104 months in asymptomatic patients and documented 91.6% patency. In their study, they also documented that the constrictive response induced by intra-graft infusion of serotonin was identical between radial arteries and ITAs implying that the increased vasoreactivity seen at the time of harvest of radial arteries is significantly attenuated over time.

In two prospective randomized single centre clinical trials, Buxton and colleagues compared the radial artery versus a second ITA in 285 young patients or to a saphenous vein in 153 older patients (age > 70 years). Repeat angiography was performed at various time intervals over a five-year period in a total of 114 patients. Five-year patency rates between radial artery and right ITA were 95% versus 100%, respectively, and those between radial artery and saphenous vein were 86% versus 95%.

Risk factors for radial artery occlusion from the literature include competitive flow from the native vessel, peripheral vascular disease history, diabetes and smoking. To date, due to low event rates, no studies have been adequately powered to prospectively demonstrate clinical benefit of calcium channel blockers (used to prevent arterial graft spasm, particularly in radial arteries) or lipid lowering therapy on arterial graft occlusion rates.

Clinical Studies
In a perioperative study comparing patients receiving left ITA + radial to those receiving bilateral ITA grafts, Borger and colleagues demonstrated similar perioperative and intermediate survival but less sternal wound infection and blood transfusion in patients receiving radial grafts.\(^{(206)}\) Acar and Carpentier showed 5-year actuarial survival of 91.6% and freedom from angina of 88.7% among patients receiving radial artery grafts in their initial cohort of radial arteries harvested in the modern era.\(^{(207)}\) In the two clinical trials by Buxton, no differences in freedom from cardiac events were noted between the three conduits, although these studies were somewhat underpowered for clinical endpoints at the interim 5-year follow-up.\(^{(205)}\)

Calafiore and colleagues followed 149 patients with bilateral ITA grafts and 139 patients with left ITA and radial grafts over eight years.\(^{(208)}\) The groups were equivalent in terms of late survival and freedom from cardiac events. Amano and colleagues prospectively followed a cohort of 459 patients receiving radial artery grafts and found three year survival of 97.2% and event-free survival of 89.6%.\(^{(200)}\)

In a well designed epidemiologic study, Zacharias and colleagues followed two cohorts of 925 propensity matched patients over six years using administrative data sources for late outcomes.\(^{(209)}\) One group received left ITA and veins while the second received left ITA, radial artery and veins. The groups were propensity matched on a large number of demographic and anatomic characteristics. In the propensity matched comparison, patients receiving radial artery harvesting had superior six-year survival (92.1% radial, 86.8% vein) and this effect was seen in all relevant subgroups. In particular diabetics, younger patients, and women derived significant survival benefit.
from radial harvesting. Among patients undergoing angiography for symptom recurrence, there was a trend towards better radial artery patency as well.

**Right Gastroepiploic Artery (RGEA)**

The use of the GEA in CABG was popularized by Pym as an alternative arterial graft in 1984. (210;211)(71-75) The GEA has been primarily used as an in-situ graft in the region of the RCA as a means to achieve total arterial revascularization in conjunction with bilateral ITA grafting or as a second arterial graft for patients with contraindications for bilateral ITA grafts. The cellular and physiological studies of the gastroepiploic artery suggest that it is similar to the radial artery in that it does not possess elastic layers in its media. (212) However, it is also similar to the ITA in that the media layer is thinner with less smooth muscle. The RGEA is more technically challenging to use as a bypass graft than other arterial conduits due to the fragile quality of the artery and the often small diameter of the vessel at the site of distal anastomosis. The RGEA reacts more strongly to the vasoconstrictors K\(^+\), thromboxane A\(_2\), endothelin-1, and norepinephrine than the ITA. (213)

The harvest technique entails nasogastric decompression and extension of the median sternotomy incision for a few centimetres to perform a limited upper midline laparotomy. Through this, the artery is harvested from close its origin at the gastroduodenal artery to its distal extent which can be quite variable but is typically two-thirds along the greater curvature of the stomach. The gastroepiploic artery is most commonly used as an in-situ graft brought either in front of or behind the stomach and
left lobe of the liver. It is tunnelled through an incision in the diaphragm and usually used to supply the right coronary artery system. It may also be used for the left anterior descending and distal circumflex system if there is adequate length. The RGEA can also be used as a free graft either from of the aorta or more commonly from of the internal mammary artery. Previous abdominal surgery may complicate conduit harvest. Prior gastric surgery, interventional radiology therapies directed towards this vessel, or documented mesenteric vascular insufficiency absolutely contraindicate the use of this vessel as a conduit.

**Angiographic Studies:**

Patency studies have generally shown excellent early patency for this conduit but the longer term patency outcomes have been similar to those of the saphenous vein. Patency results at 1 year are generally between 90-95%, at 5 years 80-90% and at 10 years, 60-70%. (214-219) Suma and colleagues showed RGEA graft patency of 96.6% at 1 month, 91.4% at 1 year, 80.5% at 5 years, and 62.5% at 10 years.(219) Causes of late occlusion were primary anastomotic stenosis and anastomosis to a less critically stenosed coronary artery. A small randomized trial comparing early RGEA and radial artery patency by Santos and colleagues showed a one-year patency rate of 89.6% (26/29) for RA and 68.9% (20/29) for RGEA (P=0.025).(220) A recent study by Takahashi and colleagues showed poorer patency for the RGEA grafted to the LAD territory than the left circumflex coronary territory where graft patency was 58.8% among 17 cases with an anastomosis to the left anterior descending artery and 93.3%
among 15 cases with an anastomosis to the circumflex artery. Voutilainen and colleagues showed a 5-year RGEA patency of 82% in 31 patients. Patency was decreased when the target vessel had a less than 70% stenosis.

Hirose and colleagues showed in a series of 1000 patients, angiography was performed on 437 patients within 1 year after operation and in 221 patients more than 1 year postoperatively. The actuarial 1-, 3-, and 5-year GEA graft patency rates were 98.7%, 91.1%, and 84.4%, respectively, and the actuarial 1-, 3-, and 5-year LIMA graft patency rates were 99.6%, 98.8%, and 97.0%, respectively (p < 0.0005).

**Clinical Studies:**

In the series by Hirose, actuarial 3- and 5-year cardiac event-free rates were 91.2% and 84.2%, respectively. Actuarial 3- and 5-year survival rates were 96.6% and 92.6%, respectively. Given the unclear benefits of third and fourth arterial grafts on survival, the additional operative time required to harvest a gastroepiploic artery, and the involvement of an additional body cavity with potential abdominal complications has limited the use of this conduit to a small number of centers mostly in Japan.

**Inferior Epigastric Artery (IEA)**

The inferior epigastric artery is a branch of the external iliac artery that runs superiorly in the rectus sheath. Histologically, it is similar to the RGEA but has a smaller lumen.
and is more prone to intimal hyperplasia at its origin at the time of harvest.\textsuperscript{(223)} It is variable in its location relative to the rectus muscle.

Puig first reported the use of the IEA as a coronary bypass conduit in 1990.\textsuperscript{(224)} A paramedian incision beginning below the umbilicus is often used to approach the IEA, although it may also be approached from the midline. The major limiting factor of the IEA is a relatively short usable length (mean, 11.9 ± 2.6 cm)\textsuperscript{(225)} with considerable variability in its usable length from patient to patient. It is primarily used to graft diagonal or intermediate branches. Calafiore and colleagues place the proximal anastomosis to an in situ internal thoracic artery rather than the aorta.\textsuperscript{(226)} Obesity, prior lower abdominal surgery or coexisting illness potentially requiring abdominal surgery are relative contraindications to the use of the IEA. Complications from IEA harvest include rectus muscle hematoma or necrosis and necrosis of the overlying skin, particularly in conjunction with bilateral ITA harvest.

\textit{Angiographic and Clinical Studies}

In a series by Calafiore, 20 of 21 (94.1\%) IEA conduits were patent at a mean 9.5 months of follow-up.\textsuperscript{(226)} Buche and colleagues studied 135 inferior epigastric artery grafts in the early post-operative period and showed 98\% patency.\textsuperscript{(227)} Seventy-seven patients underwent a second angiographic restudy at a mean of 8.5 months after the operation revealing 92\% patency. A further 29 grafts were re-evaluated at a mean of 25 months revealing 86\% patency. There are no long-term clinical studies of IEA grafts.
Summary of Conduit Selection in Coronary Surgery

Use of an ITA, usually the left, to revascularize the LAD territory is well established and is a routine element of coronary bypass surgery. The preponderance of evidence to date suggests that use of the right ITA and radial artery are safe and associated with improved early graft patency versus saphenous vein grafts. Given its favourable vascular biology and associated potential survival advantage, the right ITA would appear to be an ideal second arterial graft. The right ITA is optimally used as an in situ graft in younger non-obese, non-diabetic patients for important target vessels with fairly high grade stenosis (>70%). However, concerns about the devastating complication of sternal wound infection and conduit length have prevented widespread use of this conduit. Reports from the Society of Thoracic Surgeons database indicate that bilateral ITA use occurs in less than 2.8% of all isolated coronary bypass procedures between 2002 and 2004 despite the general consensus that right ITA patency is superior to vein grafts. (46) No large-scale randomized clinical trials have compared saphenous vein graft outcomes to either of the two most commonly used secondary arterial grafts (RITA and radial artery). Tables 1.4. and 1.5. compare the biologic properties and harvest complications of these two conduits while patency data is presented in Table 1.1.

It is in this context that the radial artery has gained popularity. With a usable length that is consistently adequate to reach virtually all target vessels, simple harvest technique which can be done concomitantly during left ITA harvest, and infrequent donor-site complications, implementation of the radial artery is limited today.
predominantly by concern about peri-operative graft spasm and diffuse narrowing in
the setting of competitive flow.

1.5. Study Hypotheses

Founded in the belief that patency is a true surrogate marker for future clinical events
after coronary bypass surgery, the studies presented in this thesis seek to identify
methods to improve graft patency based on interventions performed in the operating
room at the time of surgery. The first series of studies aim to determine the best
technique to identify grafts with technical error in the operating room so that these may
be immediately corrected. The second series of studies seek to clarify the role of the
radial artery as a bypass graft.

STUDY HYPOTHESIS 1

Intraoperative graft assessment with indocyanine green angiography is feasible
and provides high quality anatomic detail that is superior to currently used
methodologies to identify graft problems.

STUDY HYPOTHESIS 2

Radial artery grafts will have superior patency than saphenous vein grafts.
Patient and target vessel characteristics have a significant effect on graft patency,
and due to their intrinsically distinct biology, the factors for graft failure between
graft types will be different.
1.6. Chapter Previews

Preview to Chapter 2

In order to ascertain the current utilization of graft assessment technologies, arterial grafting and off-pump bypass procedures, we surveyed the entire population of Canadian cardiac surgeons using mailed questionnaires. We also attempted to identify current physician attitudes regarding innovative techniques of coronary revascularization to determine barriers to their adoption.

Preview to Chapter 3

The success of coronary bypass surgery is dependent on the construction of a technically perfect graft to coronary anastomosis. At present, no single technique of graft assessment is routinely used in coronary surgery despite studies indicating that technical errors compromise a significant number of bypass grafts. In this chapter, we perform preliminary (Phase I-II) human investigations of a novel intra-operative imaging modality using a fluorescent dye, indocyanine green, that can create an angiogram in the operating room without the use of x-ray. This technology was initially developed at the National Research Council of Canada to study the microcirculation and later commercialized by Novadaq Technologies Incorporated. The purpose of these investigations was to verify safety of the technique, determine the
optimal dye dosages, the quality of the images comparing different conduit types and
target territories, the rate of graft revision based on indocyanine green angiographic
findings and the inter-rater reliability of this intraoperative angiography technique using
a single prospective cohort study design.

Preview to Chapter 4

In Chapter 3, we demonstrated that the new ICG angiography was feasible, reliable and
provided useful clinical information leading to graft revision in several instances. The
current clinical standard to assess graft patency in the operating room is transit-time
ultrasonic flow, a technique that does not create a visible angiogram but instead
provides volumetric flow rate and flow pattern. There has been little validation of this
technique against x-ray angiography, the true reference standard. In order to determine
which technology was superior, we performed a prospective trial comparing of the
diagnostic accuracy of ICG angiography to the current clinical-standard, transit time
ultrasonic flow, using x-ray angiography as a standard reference.

Preview to Chapter 5

In this chapter we pool data from previous studies of ICG angiography to determine if
use of intraoperative graft imaging can potentially mitigate myocardial injury during
coronary artery bypass surgery. We compare myocardial injury, as defined by post-
operative peak cardiac enzyme release, in the cohort of patients who underwent
intraoperative ICG angiography to those patients who did not receive intraoperative imaging. In order to adjust for baseline characteristics in this non-randomized study, we performed multiple methods of multivariate adjustment including logistic regression and propensity-matching.

Preview to Chapter 6

In the sixth chapter of this volume, we focus our attention on the impact of conduit selection on early graft patency. While the use of the left internal thoracic artery graft to bypass the anterior circulation of the heart is well established and has proven survival benefit, incremental benefit of using other arterial conduits versus the more commonly used saphenous vein has not been proven using clinical trial methodology. In the first large-scale multicenter randomized clinical trial of its kind, we compare the one-year patency of saphenous vein grafts to radial artery grafts. The purpose of this study was to determine if radial artery bypass grafts had superior graft patency compared to saphenous vein grafts. The trial uses a unique methodology in that within patient randomization is performed and the two study conduits (radial and vein) are randomized to different coronary territories in the same patient.

Preview to Chapter 7
In this chapter, we formally study the interaction between the target vessel characteristics and graft patency. Using data from the clinical trial presented in Chapter 6, we perform a regression analysis that accounts for the complex clustering of the data from the radial artery patency study. We specifically examine the impact of the size of the target vessel and the severity of the proximal stenosis in the target vessel on one-year arterial and vein graft patency. Using this model, we determine expected patency rates for radial artery and saphenous vein conduits for a variety of patient demographic and anatomic characteristics.

Preview to Chapter 8

In the final chapter of this volume, we synthesize data collected in the previous chapters to develop a rational approach to coronary bypass surgery that will maximize graft patency. We discuss future studies and potential therapeutic targets to enhance graft patency.
Table 1.1. Comparative Protocol-Based Patency Studies of ITA, Radial Artery and Saphenous Vein Grafts

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Follow-up Interval</th>
<th>Saphenous Vein Grafts (No.)</th>
<th>Proportion Occluded (%)</th>
<th>Left ITA Grafts (No.)</th>
<th>Proportion Occluded (%)</th>
<th>Right ITA Grafts (No.)</th>
<th>Proportion Occluded (%)</th>
<th>Radial Artery Grafts (No.)</th>
<th>Proportion Occluded (%)</th>
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<td>4.1</td>
<td>22</td>
<td>4.1</td>
<td>22</td>
<td>4.1</td>
<td>29</td>
<td>2.5</td>
</tr>
<tr>
<td>Hirose (218)</td>
<td>2002</td>
<td>3-5 Year</td>
<td>182</td>
<td>9.9</td>
<td>234</td>
<td>2.1</td>
<td>66</td>
<td>3</td>
<td>89</td>
<td>11.9</td>
</tr>
<tr>
<td>Calafiore (208)</td>
<td>2002</td>
<td>3-5 Year</td>
<td>38</td>
<td>0</td>
<td>38</td>
<td>0</td>
<td>38</td>
<td>0</td>
<td>101</td>
<td>1</td>
</tr>
<tr>
<td>Iaco (228)</td>
<td>2001</td>
<td>3-5 Year</td>
<td>48</td>
<td>9</td>
<td>48</td>
<td>9</td>
<td>48</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acar (207)</td>
<td>1998</td>
<td>3-5 Year</td>
<td>48</td>
<td>9</td>
<td>48</td>
<td>9</td>
<td>48</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldman (127)</td>
<td>2004</td>
<td>10-year</td>
<td>1025</td>
<td>39</td>
<td>137</td>
<td>15</td>
<td>137</td>
<td>15</td>
<td></td>
<td></td>
</tr>
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</table>
Table 1.2.
Summary of findings from studies of intraoperative graft imaging

<table>
<thead>
<tr>
<th>Study</th>
<th>On or Off-Pump Surgery</th>
<th>Imaging Type</th>
<th>Revision Rate Per Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>D'ancona 2000 (239)</td>
<td>Off-pump</td>
<td>TTF</td>
<td>7.6% (409)</td>
</tr>
<tr>
<td>Groom 2001 (240)</td>
<td>Off-pump</td>
<td>TTF</td>
<td>7.2% (125)</td>
</tr>
<tr>
<td>Hirotani 2001(241)</td>
<td>Off-pump</td>
<td>TTF</td>
<td>7% (171)</td>
</tr>
<tr>
<td>Jakobsen 1999 (242)</td>
<td>Off-pump and On-pump</td>
<td>TTF</td>
<td>1.8% (280)</td>
</tr>
<tr>
<td>Kim 2005 (243)</td>
<td>Off-pump</td>
<td>TTF</td>
<td>5.1% (58)</td>
</tr>
<tr>
<td>Kjaergard 2004 (244)</td>
<td>Off-pump and On-pump</td>
<td>TTF</td>
<td>2% (217)</td>
</tr>
<tr>
<td>Leong 2005 (245)</td>
<td>Off-pump</td>
<td>TTF</td>
<td>5.1% (116)</td>
</tr>
<tr>
<td>Mujanovic 2002 (246)</td>
<td>Off-pump and On-pump</td>
<td>TTF</td>
<td>4.5% (440)</td>
</tr>
<tr>
<td>Sanisoglu 2003 (247)</td>
<td>Off-pump</td>
<td>TTF</td>
<td>5% (20)</td>
</tr>
<tr>
<td>Walpoth 1998 (248)</td>
<td>Off-pump</td>
<td>TTF</td>
<td>6.5% (46)</td>
</tr>
<tr>
<td>Rubens 2002 (110)</td>
<td>Off-pump and On-pump</td>
<td>ICG</td>
<td>5% (20)</td>
</tr>
<tr>
<td>Taggart 2004 (249)</td>
<td>Off-Pump</td>
<td>ICG</td>
<td>4% (200)</td>
</tr>
<tr>
<td>Reuthebuch 2004 (250)</td>
<td>Off-pump</td>
<td>ICG</td>
<td>10% (38)</td>
</tr>
<tr>
<td>Balacumaraswami 2005 (251)</td>
<td>Off-pump</td>
<td>ICG</td>
<td>8 (100)</td>
</tr>
<tr>
<td>Sonmez 2003 (97)</td>
<td>On-pump</td>
<td>Thermal Angiography</td>
<td>1% (1401)</td>
</tr>
<tr>
<td>Falk 1995 (252)</td>
<td>On-pump</td>
<td>Thermal Angiography</td>
<td>1.6% (370)</td>
</tr>
<tr>
<td>Louagie 1998 (253)</td>
<td>On-Pump</td>
<td>Pulsed Doppler Flow</td>
<td>2% (85)</td>
</tr>
<tr>
<td>Lin 2000 (254)</td>
<td>Off-pump</td>
<td>Pulsed Doppler Flow</td>
<td>8.5% (35)</td>
</tr>
<tr>
<td>Hol 2002 (255)</td>
<td>Off-pump</td>
<td>X-ray angiography</td>
<td>8.7% (45)</td>
</tr>
<tr>
<td>Mack 1999 (256)</td>
<td>Off-pump</td>
<td>X-ray Angiography</td>
<td>3% (100)</td>
</tr>
</tbody>
</table>
Table 1.3.
Summary of Anatomic and Functional Characteristics of Arterial Grafts

<table>
<thead>
<tr>
<th>Artery Type</th>
<th>Wall Thickness and Hyperplasia</th>
<th>Structure</th>
<th>Propensity for Spasm</th>
<th>Incidence of Atherosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMA</td>
<td>+++</td>
<td>Elastic</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>IEA</td>
<td>+</td>
<td>Muscular/elastic</td>
<td>Low</td>
<td>May be higher</td>
</tr>
<tr>
<td>GEA</td>
<td>++</td>
<td>Muscular</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>RA</td>
<td>++++</td>
<td>Muscular</td>
<td>High</td>
<td>May be higher</td>
</tr>
</tbody>
</table>
Table 1.4.
Comparative Biologic Properties of Right ITA and Radial Artery

<table>
<thead>
<tr>
<th></th>
<th>Right ITA</th>
<th>Radial Artery</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td>More elastic layers, less smooth muscle</td>
<td>Less elastic layers, more smooth muscle</td>
<td>(155;163;257)</td>
</tr>
<tr>
<td>Plaque at time of</td>
<td>1%</td>
<td>5%</td>
<td>(258;259)</td>
</tr>
<tr>
<td>Harvest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contractile Response</td>
<td>Lesser</td>
<td>Greater</td>
<td>(154)</td>
</tr>
<tr>
<td>to Vasoconstrictors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelium Dependant</td>
<td>Equal</td>
<td>Equal</td>
<td>(158;159)</td>
</tr>
<tr>
<td>Vasorelaxation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelium</td>
<td>Equal</td>
<td>Equal</td>
<td>(158;159)</td>
</tr>
<tr>
<td>Independent Vasorelaxation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO production</td>
<td>Greater</td>
<td>Lesser</td>
<td>(148;157)</td>
</tr>
</tbody>
</table>
Table 1.5. Incidence of Harvest Complications after Bilateral ITA and Radial Artery Harvest

<table>
<thead>
<tr>
<th></th>
<th>Bilateral ITA</th>
<th>Radial Artery</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic</td>
<td>50-65% (&lt;3 Months) 20-50% (3-12 Months)</td>
<td>5-10% (&lt;3 Months) &lt;3% (3-12 Months)</td>
<td>(181;238;260-262)</td>
</tr>
<tr>
<td>Infection</td>
<td>4-12% (Superficial) 1.3-5% (Deep)</td>
<td>&lt;1%</td>
<td>(191;192;233;238;260;261;263)</td>
</tr>
<tr>
<td>Ischemia</td>
<td>N/A</td>
<td>&lt;0.1%</td>
<td>(238;260;261)</td>
</tr>
</tbody>
</table>
Figure 1.1.
Schematic Representation of Transit-Time Flow Measurement

Ultrasound waves are generated by crystal #1 that propagate in the same direction as blood flow reflect off the reflector and are absorbed at crystal #2 (Transit Time #1). Simultaneously, ultrasound waves from crystal #2 are transmitted against the direction of blood flow and captured by crystal #1 (Transit Time #2). The difference between the two transit times allows calculation of flow velocity which, based on fixed vessel diameter ‘D’ is converted into a volumetric rate of flow.
CHAPTER 2.

Utilization of Technology in Coronary Surgery: Results of a Population-Based Survey of Canadian Heart Surgeons

2.1 Abstract

**Background:** Multiple arterial grafting (MAG) and off-pump coronary artery bypass (OPCAB) have been proposed to improve long term clinical outcomes and decrease perioperative morbidity and resource utilization. However, neither strategy is widely used in Canada. The purpose of this study was to determine the current utilization of multiple arterial grafting and OPCAB in Canada and determine why surgeons have not widely adopted these techniques.

**Methods and Results:** The study was a population-based survey of all adult Canadian cardiac surgeons in practice longer than one-year. Eligible division heads and surgeons were contacted by mail. Most surgeons performed multiple arterial grafting in less than 5% of coronary bypass cases. Of 19,806 isolated coronary bypass surgeries performed by respondents in Canada last year, 3164 (16.0%) were performed off-pump. Over 50% of Canadian surgeons performed OPCAB in less than 5% of coronary cases, and only 17% of surgeons performed OPCAB in more than 25% of coronary cases. Only four responding centers performed OPCAB in more than 25% of cases. Respondents were divided into those who performed less than 5% of cases off-pump (=Non-Adopters), 5-25% off-pump (=Intermediate Users) or greater than 25% off-pump (=Enthusiasts).
Mean number of distal anastomoses in off-pump cases were 1.7±0.6, 1.6±0.6, 3.3±0.5 for non-adopters, intermediate users and enthusiasts, respectively, p=0.001. Eleven percent of non-adopters, 55% of intermediate users and 81% of enthusiasts believed OPCAB improved clinical outcomes (p<0.0001). Only 23% of all respondents felt OPCAB utilization would increase in the next five years.

**Conclusions**: Concerns regarding incomplete revascularization and lack of proven clinical benefit have limited OPCAB to being performed routinely by only a small number of surgeons in Canada.
2.2 Background

Coronary bypass surgery is an effective treatment for severe coronary heart disease. In the past two decades, despite a dramatic increase in the risk factor profile of coronary bypass patients, operative mortality and morbidity have declined significantly. (264) These improvements have been ascribed to systematic advances in surgical technique and strategies of myocardial protection that prevent injury to the arrested heart. (265) Until recently, it has been standard practice to perform coronary bypass on the arrested heart, which provides a still operating field for the construction of fine anastomoses. Despite the tremendous success of coronary artery bypass grafting (CABG) with this technique, significant concern remains regarding the deleterious systemic effects of cardiopulmonary bypass. In particular, concerns regarding neurologic injury, renal dysfunction, and systemic inflammatory response have led surgeons to attempt coronary bypass surgery without cardiopulmonary bypass. (266-270)

New enabling technologies such as epicardial stabilizers have made it possible to perform coronary bypass surgery on the beating heart without cardiopulmonary bypass (i.e. off-pump). Off-pump coronary artery bypass (OPCAB) has been shown in several small non-randomized trials to decrease renal dysfunction, neurological injury, overall morbidity, resource utilization, and costs in certain patients compared to on-pump CABG. (271-273) Several other studies, including two small randomized trials have been equivocal with regard to these variables. (274-277) Two recently published
randomized controlled trials designed to assess graft patency have provided contradictory information regarding patency outcomes after OPCAB.(13;14) 

Despite the lack of strong evidence to support the use of one technique over the other, significant attention has been provided by the lay press to promote the use of off-pump surgery and this has led to demand for this technique by referring cardiologists and patients.(278) The primary objective of this investigation was to determine the current utilization of off-pump surgery in Canada. Secondary objectives included identifying factors leading to patient selection for off-pump surgery, assessing the perceived completeness of revascularization with off-pump surgery, and assessing surgeon attitudes towards the clinical benefits and future of off-pump surgery.

2.3 Methods

The study consisted of a population-based survey of Canadian cardiac surgeons. Eligible cardiac surgeon names and addresses were derived from the Canadian Medical Directory, the Canadian Cardiovascular Society (www.ccs.ca), and the Canadian Society of Cardiac Surgeons and verified against two industry-sponsored databases. Every cardiac surgeon performing any adult surgery and in active practice in Canada for more than one year was considered eligible. All Canadian cardiac surgeons were contacted by regular post mail with a letter from the study authors and a three page survey form. The Division Head of cardiac surgery at each hospital was also identified and received an expanded questionnaire which assessed more specific institutional level
data. Surgeons involved in the study design were excluded. A total of 141 surgeons were initially contacted to participate in the survey. Each surgeon was allotted a unique identifier code for tracking purposes. The survey assessed utilization and surgeon attitudes towards beating heart surgery according to 60 unique domains. The expanded Division Head questionnaire assessed another 17 domains at the institutional level and was administered to 33 hospital Division Heads. The survey requested information regarding the period between January 1, 2002 to December 31, 2002. A predetermined response rate of 80% for this survey was determined to provide an adequate sample of the study population. Returned survey forms were entered in a blinded fashion. Data was coded as binomial, ordinal or continuous variables as deemed appropriate. Discrete variables were analyzed using the $\chi^2$ test and continuous variables were analyzed with Student’s t-test or one-way ANOVA adjusted for equal or unequal variances where appropriate.

### 2.4 Results

Of the initial 141 study questionnaires initially sent, 15 surgeons were deemed ineligible because they were retired, in practice less than one year, or they did not practice any adult cardiac surgery. Hence, 126 questionnaires were sent to eligible surgeons and 98 were completed and returned (78% response rate). Thirty-three surgeons were sent the expanded division head questionnaire, of which there were 29 responses (88% response rate). Two of four non-responding institutions and 13 of 28 non-responding surgeons were from the province of Quebec.
Surgeon Demographics, Training, and Referral Patterns:

The median length of time in practice for responding Canadian cardiac surgeons was 13 years with a range of 2 to 35 years. Fifty-nine percent, 40% and 20% of Canadian surgeons had been in practice for at least 10, 15 and 20 years respectively. Among respondents, 87% of practicing cardiac surgeons did not have any formal training in beating heart surgery during their residency or fellowship. Of 13 respondents who had formal OPCAB surgery training, 12 had been in practice fewer than 5 years. Ten percent of division heads (3/29) indicated that their hospital had a policy of referring patients selected for off-pump surgery to surgeons with an expertise in the technique. Seventy-eight percent of centers that performed any off-pump surgery used reusable footplate-type retractor systems for their off-pump cases while 22% of centers used disposable suction-type retractors.

Multiple Arterial Grafting Utilization:

Surgeons were asked to identify the proportion of isolated coronary bypass procedures they perform with two or more arterial grafts. Results are presented in Figure 2.1, stratified by off-pump or on-pump technique. The majority of surgeons performed multiple arterial grafting in less than 25% of cases and most commonly less than 5% of cases. Less multiple arterial grafting was performed in off-pump cases than on-pump cases.

Off-Pump Surgery Utilization:

Responding centers performed a total of 19,806 isolated coronary bypass operations during the study period. Off-pump surgery was performed in 3,164 (16.0%) of these
cases. Among OPCAB cases, only 41 were performed through a mini-thoracotomy incision. At the institutional level, four of 29 responding centers (13.8%) performed more than 25% of their CABG cases on the beating heart. These four centers accounted for over 50% of all off-pump cases performed in Canada. The mean percent (± standard deviation) of cases done on the beating heart was 57.1 ± 6.9% at these four institutions, versus 8.1 ± 6.6% at the remaining 25 centers, \( p = 0.02 \). In total, four centers (13.8%) performed more than 25% of cases off-pump, 16 centers (55.2%) performed 5 to 25% of cases off-pump, and 9 centers (31.0%) performed less than 5% of cases off-pump.

Utilization of off-pump surgery also varied widely among individual respondents. Surgeons were divided into three groups, \textit{Non-Adopter} surgeons were who performed off-pump surgery in less than 5% of their cases, \textit{Intermediate User} surgeons, who performed off-pump surgery in 5% to 25% of their cases, and \textit{Enthusiast} surgeons who performed off-pump surgery in more than 25% of their cases. Fifty-five percent of respondents were \textit{Non-Adopters}, 28% of respondents were \textit{Intermediate Users}, and 17% were \textit{Enthusiasts}. (See Figure 2.2.) Nineteen percent of respondents reported they never perform beating heart surgery. Respondents were separated according to whether they have been in practice more or less than ten years to determine if there were surgeon-seniority related differences in practice pattern. (See Figure 2.2.) No significant differences according to surgeon seniority were observed, \( p=0.9 \). Ninety-six percent of respondents felt that exposure off-pump surgery training was an important part of a resident’s training experience. Among 13 surgeons formally trained
in OPCAB techniques, eight were Non-Adopters (62%), four were Intermediate Users (31%) and only one was an OPCAB Enthusiast (6%).

**Patient Selection:**

Surgeons were asked to choose which patient-related features they felt should lead to the selection of an off-pump surgical strategy over an on-pump strategy. (See Table 2.1.) Seventy-two percent of respondents felt that patients with severe calcification of the ascending aorta should undergo off-pump surgery. In lesser proportions, the presence of chronic renal failure, cerebrovascular disease and advanced age were also associated with the selection of an off-pump operation. Diffuse distal vessel disease was cited as a strong indication for selection of a conventional on-pump bypass operation over a beating heart operation. Other preoperative risk factors associated, to a lesser degree, with the selection of an on-pump procedure included emergent operation, severe left ventricular dysfunction and left main coronary artery disease. (See Table 2.1.)

**Adequacy of Revascularization:**

Seventy percent of responding surgeons believed that off-pump surgery was associated with an increased incidence of incomplete coronary revascularization. Surgeons were asked, on average, the number of distal anastomoses performed in on-pump and off-pump isolated coronary bypass cases. The mean number (± standard deviation) of distal anastomoses was 3.6 ± 0.6 in on-pump cases and 2.2 ± 0.7 for off-pump cases, p < 0.0001. The mean number (± standard deviation) of distal anastomoses for non-
adopter surgeons was 3.6 ± 0.5 for on-pump cases and versus 1.7 ± 0.6 for off-pump cases, p < 0.0001. (See Figure 2.3.) This discrepancy in number of distal anastomoses was also seen in the intermediate user group. However, the mean number (± standard deviation) of distal anastomoses among enthusiast surgeons was 3.5± 0.6 for on-pump cases versus 3.3 ± 0.5 for off pump cases, p = 0.1. The overall p-value for this analysis by ANOVA was 0.008.

Approximately 80% of non-adopter and 78% of intermediate user surgeons felt that incomplete revascularization was more common in off-pump surgery than on-pump surgery. (See Figure 2.4.) Conversely, only 28% of enthusiast surgeons felt that incomplete revascularization was more common with off-pump techniques, p = 0.0001.

Intraoperative Decision-Making:
Surgeons were polled on several matters related to intraoperative decisions regarding surgical technique selection. Twenty-nine percent of surgeons who performed off-pump surgery stated that they intraoperatively converted from off-pump to on-pump coronary bypass in more than 5% of their off-pump cases. Reasons for intraoperative conversion from off-pump to on-pump coronary bypass are presented in Table 2.2. Among Non-Adopters and Intermediate-Users, 35% and 27% of surgeons, respectively, stated their conversion rate was higher than 5%, while among Enthusiasts, only 6% of surgeons had a conversion rate greater than 5%, p=0.05. Twenty-eight percent of all surgeons stated they have converted from on-pump to off-pump coronary bypass to avoid a severely calcified ascending aorta in at least one case. In total, 11% of
surgeons stated they intraoperatively convert from on-pump to off-pump surgery in more than 5% of their on-pump cases.

**Attitudes Towards Off-Pump Surgery:**
Surgeon attitudes toward the clinical impact and future of beating heart surgery were assessed. (See Figures 2.5. and 2.6.) When asked if surgeons felt off-pump CABG improved clinical outcomes, 64% of respondents did not believe that off-pump CABG improved clinical outcomes. By practice pattern, 78% of Non-Adopters, 52% of Intermediate Users, and 17% of Enthusiasts did not feel off-pump surgery improved clinical outcomes, \( p = 0.001 \). (See Figure 2.5.) A similar pattern was observed in surgeons opinions regarding resource utilization, where 90% of Non-Adopters, 44% of Intermediate Users, and 20% of Enthusiasts did not feel that off-pump surgery decreased resource utilization, \( p = 0.001 \).

Surgeons were also asked whether they thought that the use of off-pump surgery would increase, decrease, or remain the same in the next five years. Twenty-three percent of respondents felt off-pump surgery use would increase, 25% felt it would decrease, and 52% felt that it would remain the same over the next five years. (See Figure 2.7.) There were no major differences between Non-adopters, Intermediate Users, and Enthusiasts for this question, \( p = 0.3 \).

**Use of Intraoperative Graft Evaluation Technologies**
Use of graft assessment technologies was more common among surgeons for off-pump cases versus on-pump cases in Canada. As seen in Figure 2.8., the most commonly
used method of graft assessment was transit-time ultrasonic flow, which was used routinely by 26% of surgeons in off-pump cases and 8% of surgeons in on-pump cases, p<0.05. Doppler based methods were used in 10% and 8% of off-pump and on-pump cases respectively. A small proportion (3%) of surgeons routinely used early post-operative x-ray angiography to verify off-pump graft patency.

2.5 Discussion

Multiple Arterial Grafting:
The usage of multiple arterial grafting by respondents in this study was somewhat lower than expected with the majority of surgeons using this strategy less than 25% of the time. Although we did not poll surgeons directly on their decision making process regarding arterial grafting, we speculate that the lack of objective clinical trial evidence may be the main barrier to adoption.

Off-Pump Surgery:
Off-pump coronary bypass surgery has gained significant implementation in the United States. Industry groups have suggested that the true proportion of off-pump surgery in the United States is greater than 25%. The results of the current study show that the proportion of off-pump cases in Canada is significantly lower. Off-pump coronary artery bypass was performed in only 16.0% of isolated coronary bypass cases in Canada in 2002. The causes for decreased utilization of off-pump coronary bypass in Canada versus the United States are multifactorial and may be partially related to structural differences between the health care systems of these countries. In the United
States, a decentralized private health system, marketing pressures to attract patients with newer techniques or technologies have been speculated to play a role in the current popularity of off-pump coronary surgery. (281) In the publicly funded Canadian health care system, cardiac surgery referrals are generally regionalized to specific centers and there is rarely competition between institutions for patients. (282)

The lack of competition in the Canadian system may decrease the willingness to adopt highly marketable but unproven technologies and techniques. However, funding constraints imposed by government in the Canadian system may also delay spending on new technology and innovation. In particular, operating room technology used for OPCAB in Canada appears to be lagging behind. The use of suction-type stabilizers, which have been purported to decrease the rate of conversion to on-pump CABG and enable more complete revascularization, were used by a minority (22%) of Canadian surgeons for their OPCAB cases. (19) This may have been related to increased per-procedure costs for using such devices, which are generally disposable, versus reusable foot-plate type stabilizers. Depending on costs of cardiopulmonary bypass pump disposables and method of pump-standby, OPCAB cases with disposable stabilizers may be more expensive in operating room costs, but provide lower overall costs due to decreased blood use, ICU and hospital stay. Since most Canadian hospitals are generally funded on an annual global basis as opposed to per-patient reimbursement, these savings are often not appreciated by the institution and prohibitive costs of disposables may discourage the use of OPCAB.
In this survey, among Canadian surgeons who were not OPCAB enthusiasts (less than 25% of cases done off-pump), the mean number of distal anastomoses performed per case were significantly lower in off-pump patients. (See Figure 2.3.) While these numbers were self-reported and should be interpreted with caution, several studies have previously reported that off-pump patients receive less bypass grafts than similar on-pump patients. (283-285) Fewer distal anastomoses have been reported in OPCAB series for several reasons including hemodynamic instability, particularly while revascularizing the lateral wall of the heart, residual epicardial motion, or severely diseased, small or intramyocardial coronary vessels. (22) In these situations, surgeons must decide whether to expose the patient to the risk of conversion to an on-pump procedure or the risk of incomplete revascularization.

Since ‘completeness’ of revascularization is difficult to truly quantify, we sought to determine if surgeons in the three different utilization groups felt the incomplete revascularization was occurring more often in their own OPCAB cases versus their own on-pump cases. As expected, Non-Adopter surgeons felt that incomplete revascularization was more common in their patients undergoing OPCAB. Surprisingly, in the Intermediate User group, who performed OPCAB in up to 25% of CABG cases, nearly 80% of surgeons felt they were achieving incomplete revascularization in their own OPCAB patients. Since several clinical studies have shown that incomplete revascularization in patients with three-vessel disease leads to an elevated risk of long-term mortality, we attempted to determine why these surgeons would choose off-pump techniques. (286;287) Surgeons stated that the most important
factor for selecting off-pump surgery was severe aortic calcification, followed to a lesser degree by cerebrovascular disease, renal disease, and advanced patient age. Thus Intermediate User surgeons appear to be attempting to balance the risk of operation in morbid patients with the potential harm of incomplete revascularization by choosing on off-pump strategy. While several reports suggest that early outcomes of off-pump surgery in higher risk patients are superior, it is not known whether the long-term consequences of incomplete revascularization will be similar in on-pump and off-pump patients.(288;289)

Incomplete revascularization appears to be more prevalent during the learning curve of OPCAB surgery.(22) This learning curve applies not only to the operating surgeon, but also to the entire operating room team. Among surgeons with low OPCAB volume, i.e. the Canadian Non-Adopter majority, the learning curve may never be adequately overcome due to the lack of repetition needed to master OPCAB surgical and anaesthetic techniques. In a setting where market forces and short-term economics do not create an incentive to perform OPCAB regularly, many Canadian surgeons may be performing incomplete revascularization due to lack of experience among the whole operating room team. Since the rate of conversion from OPCAB to on-pump CABG was dramatically higher in both the Non-Adopter and Intermediate User groups, there does appear to be a general level of discomfort among these surgeons at performing OPCAB.
The implementation of off-pump surgery in Canada was both surgeon and site-dependent and appeared to be related to how the surgeon perceives this technique will benefit the patient. At present, over 50% of off-pump operations are being performed in only four centers and by a handful of enthusiast surgeons. In the hands of these surgeons, revascularization rates appear to be equivalent and these surgeons believe that patient outcomes are improved by using OPCAB. In this survey, the majority of Canadian cardiac surgeons (55%) were Non-Adopters of off-pump technology. This Non-Adopter majority did not believe that off-pump surgery improved clinical outcomes or decreased resource utilization. These surgeons may be waiting for better supporting evidence before adopting off-pump surgery more routinely. Since there is still no clear clinical evidence from multicentre randomized trials that either technique is superior, it is appropriate that off-pump surgery remains predominantly performed in centers of excellence until such data is available.

A large majority Canadian cardiac surgeons also felt that off-pump surgery utilization would not change over the next five years. This sentiment was expressed by Non-Adopter, Intermediate User and Enthusiast surgeons alike suggesting that most surgeons were confident in the case-mix they were currently practicing. Interestingly, only one of thirteen surgeons in Canada with specific training in OPCAB was an OPCAB Enthusiast. Despite the high proportion of Non-Adopter surgeons in Canada, an overwhelming majority (96%) of respondents felt that off-pump surgery training was an important part of resident training. With only a few centers actively performing off-
pump surgery, it is unlikely that all Canadian cardiac surgery residents will receive adequate exposure to this technique.

Intraoperative Graft Assessment:
The use of validated intraoperative graft imaging technologies was extremely low by surgeons performing on-pump surgery. Since perioperative graft occlusion is often a sporadic and unpredictable event that is associated with elevated morbidity, it is surprising that utilization of technologies that can identify early occlusions was so low (<10%). Barriers to adoption may include cost, lack of familiarity with the technology, difficulty using or interpreting the technology, lack of faith in the diagnostic accuracy of the technology, or potential harm to patients by invasive technologies. As expected, a greater proportion of surgeons used these technologies in more technically demanding off-pump surgery cases.

Study Limitations
There are several limitations to this study. It was a voluntary, post-mail survey of all Canadian cardiac surgeons. A high proportion (88%) of division heads contributed responses to the survey, giving an accurate estimate of OPCAB utilization throughout Canada. Although the overall response rate for the surgeon questionnaire was 78%, there were substantially more individual non-responders from the province of Quebec and the presented data may not accurately reflect surgeon opinions within that region. Otherwise, it is not known if non-responders were systematically different in their practice patterns or opinions from responders. The survey data regarding self-reported mean number of distal anastomoses and rates of incomplete revascularization were
prone to reporting biases that would tend to support a particular surgeon’s practice style. As such, these findings should be interpreted with some caution. Evidence from provincial and national registry data is likely more reliable than surgeon’s own estimates of their performance. (290)

This survey provides insight into the practice of coronary revascularization in Canada. Currently, OPCAB utilization in Canada appears to be lower than in the United States and only a small minority of surgeons and centers routinely perform this technique. The majority of Canadian surgeons do not appear convinced that the current literature or their clinical experiences support increasing the utilization of OPCAB surgery. This survey will be repeated in three to four years to determine if surgeon attitudes change with new evidence.
Tables and Figures

Table 2.1. Patient Risk Factors Identified by Surgeons for Selection of Off-Pump or On-Pump Surgery

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>% of Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Selection of Off-Pump technique over On-Pump:</strong></td>
<td></td>
</tr>
<tr>
<td>Severely Calcified Ascending Aorta</td>
<td>72%</td>
</tr>
<tr>
<td>Chronic Renal Failure</td>
<td>33%</td>
</tr>
<tr>
<td>Advanced Age</td>
<td>30%</td>
</tr>
<tr>
<td>History of Cerebrovascular Disease</td>
<td>22%</td>
</tr>
<tr>
<td><strong>B. Selection of On-Pump technique over Off-Pump:</strong></td>
<td></td>
</tr>
<tr>
<td>Diffuse Coronary Disease</td>
<td>66%</td>
</tr>
<tr>
<td>Emergent Patient Status</td>
<td>35%</td>
</tr>
<tr>
<td>Poor Ventricular Function</td>
<td>27%</td>
</tr>
<tr>
<td>Left Main Disease</td>
<td>21%</td>
</tr>
</tbody>
</table>

* Survey Respondents were allowed to chose more than one selection. Therefore, totals sum to greater than 100%.
Table 2.2. Causes of Intraoperative Conversions

<table>
<thead>
<tr>
<th>Cause</th>
<th>% of Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conversion from Off-Pump to On-Pump:</td>
<td></td>
</tr>
<tr>
<td>Hemodynamic instability <em>prior</em> to manipulation of the heart</td>
<td>9%</td>
</tr>
<tr>
<td>Hemodynamic instability <em>after</em> manipulation of the heart</td>
<td>35%</td>
</tr>
<tr>
<td>Intramyocardial target vessels</td>
<td>25%</td>
</tr>
<tr>
<td>Diffusely diseased target vessels</td>
<td>20%</td>
</tr>
<tr>
<td>Anaesthetist preference despite stable hemodynamics</td>
<td>15%</td>
</tr>
<tr>
<td>Conversion from On-Pump to Off-Pump:</td>
<td></td>
</tr>
<tr>
<td>Severely Calcified Ascending Aorta</td>
<td>28%</td>
</tr>
</tbody>
</table>

* Survey Respondents were allowed to chose more than one selection. Therefore, totals sum to greater than 100%.
Figure 2.1. Utilization of 2 or more arterial grafts by Canadian Cardiac Surgeons stratified according to ON- or OFF-Pump technique. Black bars represent ON-PUMP procedures and White Bars represent OFF-PUMP Procedures.
Figure 2.2. Utilization of Off-Pump Coronary Bypass in Canada. Solid bars represent total utilization percentages, open bars represent OPCAB utilization among surgeons in practice less than 10 years, and bars with diagonal lines represent OPCAB utilization among surgeons in practice more than 10 years. Surgeons were separated by practice pattern into non-adopters (<5% of isolated CABG cases off-pump), intermediate users (5% to 25% of isolated CABG cases done off-pump), and enthusiasts (>25% of isolated CABG cases done off-pump). No difference in off-pump utilization was seen between surgeons in practice longer than 10 years versus those in practice less than 10 years. (p = 0.9 by ANOVA)
Figure 2.3. Mean number of distal coronary anastomoses performed by study participants in the past 12 months for Off-Pump and On-Pump coronary bypass cases. Surgeons were separated by practice pattern into non-adopters (<5% of cases done off-pump), intermediate users (5% to 25% of cases done off-pump), and enthusiasts (>25% of cases done off-pump). Mean values +/- standard deviation are shown. (Overall p = 0.008 by ANOVA)
Figure 2.4. Survey Question: *Is incomplete revascularization more common in off-pump coronary bypass surgery?* Surgeons were separated by practice pattern into non-adopters, intermediate users, and enthusiasts. (Overall p = 0.001)
Figure 2.5. Survey Question: *Does Off-Pump coronary bypass improve clinical outcomes?* Surgeons were separated by practice pattern into non-adopters (<5% of cases done off-pump), intermediate users (5% to 25% of cases done off-pump), and enthusiasts (>25% of cases done off-pump). (Overall p = 0.001)
Figure 2.6. Survey Question: *Does Off-Pump coronary bypass decrease resource utilization?* Surgeons were separated by practice pattern into non-adopters (<5% of cases done off-pump), intermediate users (5% to 25% of cases done off-pump), and enthusiasts (>25% of cases done off-pump). (Overall p = 0.001)
Figure 2.7. Survey Question: *In the next five years, will Off-Pump surgery utilization increase, decrease, or stay the same?* Surgeons were separated by practice pattern into non-adopters (<5% of cases done off-pump), intermediate users (5% to 25% of cases done off-pump), and enthusiasts (>25% of cases done off-pump). (Overall p = 0.3)
Figure 2.8. Proportion of Surgeons routinely using various types of graft patency assessment stratified by ON-PUMP or OFF-PUMP surgery. Black bars represent ON-PUMP procedures and White Bars represent OFF-PUMP Procedures.
CHAPTER 3.

Improving the Quality of Coronary Bypass Surgery with Intraoperative Angiography: Validation of a New Technique

3.1 Abstract

Objectives: We report a comprehensive assessment and validation of a new intraoperative angiography technique.

Background: Technical problems at the site of the distal anastomosis compromise an underappreciated proportion of coronary bypass grafts. The absence of a systematic, validated technique to verify graft patency in the operating room represents a significant breech in quality assurance.

Methods: Fluorescent indocyanine green (ICG) dye, is excited with dispersed laser light to create an angiographic depiction of the graft, native vessel, and anastomosis. One-hundred-twenty patients underwent ICG angiography. Angiograms were reviewed for reliability and validity studies.

Results: 348 coronary bypass grafts were studied. Each ICG angiogram took 2.2±1.1 minutes to perform. ICG angiography found 4.2% of patients had significant graft problems requiring major revision. Quality of visualization was rated according to a 7-point Likert scale (1=worst, 7=best). Among conduits, saphenous veins were best visualized (mean score ±sd) 6.4±1.5 vs. 5.5±1.9 for internal mammary arteries and 4.4±2.3 for radial arteries, p=0.02. Location of distal anastomosis did not influence quality of visualization. There was high inter-rater reliability for graft revision (kappa=1.0) and graft patency (kappa=0.97) between surgeons.

Conclusions: Information from ICG angiograms led to graft revisions for technical problems in 4.2% of patients that would have otherwise gone unrecognized.
Intraoperative angiography represents an emerging tool to improve the quality of coronary bypass surgery.
IMPROVING THE QUALITY OF CORONARY BYPASS SURGERY WITH INTRAOPERATIVE ANGIOGRAPHY: VALIDATION OF A NEW TECHNIQUE

3.2 Background

Graft patency is the major determinant of survival and freedom from re-intervention after coronary bypass surgery. The construction of a technically perfect anastomosis at the time of surgery is an important determinant of graft patency. Modern coronary bypass series report perioperative graft occlusions rates as high as 12% (291;292). Technical errors in bypass graft construction by the operating surgeon are primarily responsible for these early failures. There is currently no standardized approach to identify these errors using any form of intraoperative graft assessment and it is not routine clinical practice in most centers. We present reliability studies and validation of a simple technique of intra-operative fluorescent dye angiography which provides high fidelity angiographic images similar to catheter-based x-ray angiography.

3.3 Methods and Materials

This study was a prospective evaluation of the reliability and validity of a new diagnostic imaging modality: indocyanine green (ICG) dye fluorescence angiography.

Contrast Agent

Indocyanine green is a negatively charged, polymethine tricarbocyanine dye (chemical formula C_{43}H_{47}N_{2}NaO_{6}S_{2}) with absorbance and fluorescence maxima in the near infra-red (750-1000 nanometer = 1 billionth of a meter) region, where very few
molecules exhibit intrinsic fluorescence and there is little background fluorescence. When illuminated at 806 nm, ICG fluoresces to emit light centered at 830nm.

Indocyanine green is non-covalently (95%) bound to albumin and is not nephrotoxic. It is taken up from the plasma by hepatic parenchymal cells and secreted into the bile. Indocyanine green dye is an approved drug that is used clinically in ophthalmologic and vascular procedures. Adverse reactions to ICG are uncommon. There are isolated reports of hypotension requiring fluid resuscitation and epinephrine treatment. A Japanese study reviewing complications of ICG used at doses of 25 to 75 mg in ophthalmology patients showed three patients of 2820 studied had any adverse event requiring treatment: one patient experienced pain in the injected vein, two patients had hypotension requiring treatment.(34) The maximum expected dose if ICG for performing coronary graft angiograms is less than 10 mg. An American study reviewing adverse reaction to indocyanine green angiography in 1226 ophthalmology patients found only one patient had a severe reaction. (35) There were no deaths in either study. One report from 1971 identified an increased risk of adverse reactions in uremic hemodialysis patients. (36) The LD50 after I.V. administration is greater than 50 mg/kg in animal models. The anticipated doses used for cardiac graft assessment will be less than 0.4mg/kg.

**Imaging Device**

The imaging device (Novadaq Technologies Inc., Concord, Ontario, Canada) is composed of an imaging head containing an 806 nm LASER light source and a CCD video camera equipped with an optical filter to block transmission of visible and 806 nm light while optimizing transmission of ICG fluoresced light at 830nm. Eye
protection is not required in the operating room since the LASER light energy (2.0 Watts) is dispersed. The imaging head is positioned over the exposed heart and the laser activated prior to first pass of a bolus of ICG through the field of view. Images of the coronary arteries and bypass grafts are acquired at a rate of 30 frames/second and may be viewed in real time. The near infrared light can maximally penetrate one to two millimeters of soft tissue. The fluorescence sequentially shows illumination of the graft or coronary artery lumen, a blush of the epicardium as dye passes through the microcirculation, and finally, washout through the coronary veins.

Optimal methods of dye injection for each type of graft in on-pump and off-pump coronary operations were developed for each method of dye injection by varying dye dosage and timing of the LASER. For injection into the central venous line, 1.25mg of dye (0.5cc of reconstituted dye solution) achieved excellent contrast for graft visualization. Higher doses generally caused a ‘white-out’ effect with too much fluorescence and lower doses did not provide enough contrast. Typically, contrast was seen in the graft 10s after injection into the central venous line. Injections into the aortic cannula required 2.5mg (1 cc) of dye for optimal images and contrast was seen in the graft 10-15s after injection. Direct graft injections of the reconstituted dye required a very different dosing regimen. We found that fluorescence could not be achieved unless the dye was in contact with the patient’s blood, taken from the pump or side branch of the aortic cannula. We found that a very minute amount of ICG dye (<0.0125mg) was required to achieve a high quality an image. To create the injecting solution, 2.5mg (1cc of reconstituted dye) was mixed with 1L of normal saline and
49cc of this dilute solution was mixed with 1cc of the patient’s blood to provide 50cc of injectable solution. Generally 10cc was used per injection for adequate contrast and since the graft was directly injected with dye, contrast is seen immediately after injection. Optimal image protocols are presented in Table 3.1.

Patients

All patients signed a consent form approved by the local institutional review ethics board after being approached by a study-coordinator who was not affiliated with their clinical care. Operations were performed by 6 experienced surgeons, each performing at least 200 cases per year. Exclusion criteria included allergy to ICG dye and cardiogenic shock.

Patients underwent coronary bypass surgery according to standard technique and ICG angiography was performed of all bypass grafts. Grafts deemed to be occluded by ICG angiography in the operating room were revised and operative findings were noted. Images were assessed off-line for determination of surgeon-specified image quality and inter-rater agreement.

Statistical Methods

Categorical variables are presented as proportions and percentages and continuous variables as means with standard deviations. Comparison of means for surgeon assessment of quality of visualization was performed using one-way ANOVA. Inter-rater agreement for graft revision, patency and Thrombolysis In Myocardial Infarction (TIMI) flow grade (293) was determined using Cohen’s Kappa statistic.
3.4 Results

Between September 2002 and January 2004, 120 patients were recruited. Comprehensive graft assessment was performed in all patients. Patient characteristics are reported in Table 3.2. Patients were generally representative of the overall coronary bypass population at our institution. Operative characteristics are presented in Table 3.3. In total 348 grafts were performed with a mean of 2.9 grafts per patient. The vast majority of bypasses were performed on-pump, as is our routine clinical practice. A total of 432 ICG angiograms were performed with a mean of 3.6±0.9 ICG angiograms performed per patient. Typically, we performed one angiogram for each distal anastomosis and one angiogram for all proximal anastomoses. Average time to perform one ICG angiogram was 2.2±1.1 minutes/patient. A representative angiogram of left-internal mammary artery bypass graft is presented in Figure 3.1.

Using ICG angiography, we found that 4.2% (5/120) of patients had significant graft problems requiring major anastomotic revision or new graft construction. These graft problems included: twisted vein graft (1), significant lesion in native vessel distal to the graft-coronary artery anastomosis(2), technical problems at the anastomosis (2). A representative angiogram is presented in Figure 3.2. A further 4 grafts (3.3%) required minor revision based on intraoperative findings. These included: graft repositioning (1), and extra suture to improve hemostasis (2).

Angiographic results are summarized in Table 3.4. Quality of visualization was rated according to a 7-point Likert scale(1=worst,7=best). Among conduits, saphenous veins
were best visualized (mean score ±sd) 6.4±1.5 vs. 5.5±1.9 for internal mammary arteries and 4.4±2.3 for radial arteries, ANOVA overall p=0.02. Location of distal anastomosis did not influence quality of visualization.

Inter-rater agreement among two surgeons, one experienced and one inexperienced with the technique, was 100% (Cohen’s kappa=1.0) for assessing total graft occlusion and 97% (Cohen’s kappa=0.9) for assessing graft revision when 35 ICG angiograms were reviewed off-line. Inter-rater agreement for assessing TIMI flow grade was only 60% (Cohen’s kappa = 0.4).

3.5 Discussion

With the exception of coronary artery bypass surgery, virtually all other interventions on the heart, including cardiac valve repair and coronary stenting, are accompanied by completion diagnostic imaging to ensure adequate technical result. Despite tremendous improvements in the quality of processes of care in cardiac surgery over the past decade, there is still no well accepted or broadly used technique to assess the quality of the bypass graft itself. In the current study, we determined that in a high volume academic practice, nearly 1% of internal mammary artery grafts and 3% of saphenous vein grafts required graft revision when completion indocyanine green angiography was performed as a method of intraoperative quality assessment. When analyzed by patient, 4.2% of patients required graft revision. In all cases, the lesions would have otherwise been missed by the operating room team. The clinical consequences of early
graft failure are not benign and a recent report suggests that the perioperative mortality in patients with unrecognized graft problems is over 9%. (70)

After promising pre-clinical investigations with this technique, we performed the first human studies in 2002. (110) Subsequently, we have embarked on a rigorous systematic approach to intraoperative graft patency assessment using ICG angiography. The technique showed perfect inter-rater reliability for graft patency among two surgeons, one with significant experience in the technique and one with no previous experience with the technique, suggesting that interpretation of images does not require significant training or a learning curve. There was poor inter-rater reliability for graft TIMI flow. Since most free grafts in the series were hand injected, the subjective interpretation of TIMI flow grade was dependent on the rate of injection by the surgeon or assistant, which were not standardized. Pedicled grafts were less well seen with ICG angiography, likely due to fat and muscular tissue overlying the artery, which scatters the fluorescence signal. To improve pedicled graft visualization, our current practice is to partially skeletonize the distal portion of the graft from its overlying muscle and fat. For an average coronary bypass case, the total extra time to perform intraoperative patency assessment will be 8-10 minutes, including 6 or more minutes while the aortic cross-clamp is applied.

Since ICG angiography may be able to identify most graft lesions prior to chest closure, its potential effect on early graft patency may be similar to perioperative aspirin use,
anti-lipid medications and arterial grafting. Further studies will assess the diagnostic accuracy and clinical utility of this technique.
Tables and Figures

**TABLE 3.1. Optimal Dye Injection Methods for Indocyanine Green Angiography**

<table>
<thead>
<tr>
<th>Anastomosis and Graft to be Assessed</th>
<th>Dye Delivery Method</th>
<th>ICG Dye Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distal Anastomosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-Situ Grafts On-Pump: LIMA, RIMA, GEA</td>
<td>Injection into aortic cannula</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>In-Situ Grafts Off-Pump: LIMA, RIMA, GEA</td>
<td>Injection into central venous line</td>
<td>1.25 mg</td>
</tr>
<tr>
<td>Free Grafts: SVG, Radial, free IMA</td>
<td>Direct graft injection prior to proximal anastomosis construction</td>
<td>0.0125 mg</td>
</tr>
<tr>
<td><strong>Proximal Anastomosis:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free Grafts: SVG, Radial, free IMA</td>
<td>Injection into central venous line after weaning from CPB</td>
<td>1.25 mg</td>
</tr>
</tbody>
</table>

On-pump = performed with cardiopulmonary bypass on an arrested heart
Off-pump = performed without cardiopulmonary bypass on a beating heart
ICG = Indocyanine Green
LIMA = Left Internal Mammary Artery
RIMA = Right Internal Mammary Artery
GEA = Gastroepiploic Artery
IMA = Internal Mammary Artery
SVG = Saphenous Vein Graft
CPB = Cardiopulmonary bypass
TABLE 3.2. Preoperative Patient Characteristics (n=120)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD or Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>67.6 ± 9.1</td>
</tr>
<tr>
<td>Sex: Males</td>
<td>94 (78.3%)</td>
</tr>
<tr>
<td>Females</td>
<td>26 (22.1%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>32 (26.7%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>80 (66.7%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>76 (63.3%)</td>
</tr>
<tr>
<td>Urgent Surgery</td>
<td>64 (53.3%)</td>
</tr>
<tr>
<td>Reoperation</td>
<td>2 (1.7%)</td>
</tr>
<tr>
<td>Smokers</td>
<td>69 (57.5%)</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>13 (10.8%)</td>
</tr>
<tr>
<td>NYHA Class 3 or 4</td>
<td>91 (75.8%)</td>
</tr>
<tr>
<td>Ejection Fraction &lt; 30%</td>
<td>17 (14.2%)</td>
</tr>
<tr>
<td>Preoperative MI</td>
<td>56 (46.7%)</td>
</tr>
</tbody>
</table>

NYHA – New York Heart Association
MI = Myocardial Infarction
### TABLE 3.3. Operative Data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean +/- SD or N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of bypassed vessels</td>
<td>348</td>
</tr>
<tr>
<td>Mean number of bypassed vessels</td>
<td>2.9 +/- 0.8</td>
</tr>
<tr>
<td>Off-Pump</td>
<td>4 (3.3%)</td>
</tr>
<tr>
<td>Mean Cross-Clamp Time</td>
<td>82 +/- 32 min</td>
</tr>
<tr>
<td>Mean Cardiopulmonary Bypass Time</td>
<td>112 +/- 31 min</td>
</tr>
<tr>
<td>Number of ICG Angiograms</td>
<td>432</td>
</tr>
<tr>
<td>Mean number of ICG Angiograms</td>
<td>3.6 +/- 0.9</td>
</tr>
<tr>
<td>Mean time per ICG angiogram</td>
<td>2.2 +/- 1.1 min</td>
</tr>
<tr>
<td>Conduits Revised / Conduits Studied</td>
<td></td>
</tr>
<tr>
<td>1. LIMA</td>
<td>1/119 (0.9%)</td>
</tr>
<tr>
<td>2. RIMA</td>
<td>0/8 (0%)</td>
</tr>
<tr>
<td>3. Radial artery</td>
<td>0/67 (0%)</td>
</tr>
<tr>
<td>4. Saphenous Vein Grafts</td>
<td>4/154 (2.6%)</td>
</tr>
<tr>
<td>Patients Requiring Major Graft Revision</td>
<td>5/120 (4.2%)</td>
</tr>
</tbody>
</table>
### TABLE 3.4. Validity and Reliability Studies of Indocyanine Green Angiography

<table>
<thead>
<tr>
<th>Visualization by Graft Type and Distal Territory</th>
<th>Quality of Visualization (1 = Worst, 7 = best)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Graft Type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal Mammary</td>
<td>5.5±1.9</td>
<td></td>
</tr>
<tr>
<td>Saphenous Vein</td>
<td>6.4±1.5</td>
<td>0.02*</td>
</tr>
<tr>
<td>Radial Artery</td>
<td>4.4±2.3</td>
<td></td>
</tr>
<tr>
<td><strong>Distal Territory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior Wall</td>
<td>5.1±2.3</td>
<td></td>
</tr>
<tr>
<td>Lateral Wall</td>
<td>5.1±2.1</td>
<td>0.52*</td>
</tr>
<tr>
<td>Anterior Wall</td>
<td>5.7±1.9</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inter-Rater Reliability</th>
<th>Percent Agreement</th>
<th>Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft Revision†</td>
<td>100%</td>
<td>1.0</td>
</tr>
<tr>
<td>Graft Patency‡</td>
<td>97%</td>
<td>0.9</td>
</tr>
<tr>
<td>TIMI Flow Grade</td>
<td>60%</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* One-way ANOVA for overall comparison between the three groups.
† Surgeon stated he/she would revise graft based on ICG angiogram findings
‡ Surgeon believed graft was 100% patent based in ICG angiogram
Figure 3.1. Indocyanine Green Angiograms of an in-situ left internal mammary artery (White Arrow) bypass to left anterior descending coronary artery (Black Arrow). The Distal anastomosis is well seen and denoted by the asterisk.
Figure 3.2. Indocyanine Green(ICG) Angiogram of a Saphenous Vein Graft. In panel A, there is contrast dye in the vein graft (White Arrow) but no dye enters the distal posterior descending coronary artery (Black Arrow). The distal anastomosis was reopened and an occlusive stitch was found penetrating through the posterior wall of the target coronary vessel preventing antegrade flow. The anastomosis was revised in the post-revision angiogram (panel B) contrast was observed to rapidly fill the vein graft (White Arrow) and distal coronary vessel (Black Arrow).
CHAPTER 4

A Randomized Comparison of Intraoperative Indocyanine Green Angiography and Transit-Time Flow Measurement to Detect Technical Errors in Coronary Bypass Grafts

4.1 Abstract

Background: Early coronary bypass graft failures may be preventable if identified intraoperatively. The purpose of this investigation was to compare the diagnostic accuracy of two intraoperative graft assessment techniques, transit time ultrasound flow measurement (TTF) and indocyanine green (ICG) fluorescent-dye graft angiography.

Methods: Patients undergoing isolated CABG with no contraindications for postoperative angiography were enrolled in the study. Patients were randomly assigned to be evaluated with either 1. ICG angiography (Novadaq Spy™ Angiography system) then TTF (Medtronic Medistim™ System) or TTF then ICG angiography. Patients underwent x-ray angiography on postoperative day four. The primary endpoint of the trial was to determine the sensitivity and specificity of the two techniques versus reference standard x-ray angiography to detect graft occlusion or >50% stenosis in the graft or perianastomotic area.

Results: Between February 2004 and March 2005, 106 patients were enrolled and x-ray angiography was performed in 46 patients. In total, 139 grafts were reviewed with all three techniques and 12 grafts (8.2%) were demonstrated to have >50% stenosis or occlusion by the reference standard. The sensitivity and specificity of ICG angiography to detect >50% stenosis or occlusion was 83.3% and 100%, respectively. The sensitivity and specificity of TTF to detect >50% stenosis or occlusion was 25% and
98.4%, respectively. The p-value for the overall comparison of sensitivity and specificity between ICG angiography and TTF was 0.011. The difference between sensitivity for ICG angiography and TTF was 58% with a 95% confidence interval of 30% to 86%, p=0.023.

Conclusions: ICG angiography provides superior diagnostic accuracy for detecting clinically significant graft errors versus TTF flow measurement.
A RANDOMIZED COMPARISON OF INTRAOPERATIVE INDOCYANINE GREEN ANGIOGRAPHY AND TRANSIT-TIME FLOW MEASUREMENT TO DETECT TECHNICAL ERRORS IN CORONARY BYPASS GRAFTS

4.2 Background

Currently, there is no standardized approach to intraoperative graft assessment and it is not performed routinely by most surgeons. Since graft patency is the predominant predictor of long-term survival after coronary surgery, lack of a reliable and well-validated method to assess graft patency in coronary surgery remains an important opportunity for improving quality assurance. Transit-time ultrasound flow measurement (TTF) has recently become a commonly used method of intra-operative patency assessment, particularly in off-pump coronary surgery. Despite the ease of use of this technique, authors have raised concerns regarding the diagnostic accuracy of TTF measurements in non-occlusive stenoses. After promising early clinical investigations with a novel method of intraoperative angiography using the fluorescent dye indocyanine green (ICG), we embarked on a rigorous, systematic approach to determine the optimal method of intraoperative graft patency assessment. We conducted a prospective comparison of the diagnostic accuracy of TTF and ICG angiography to determine graft failures, using x-ray angiography as a reference standard. We used a unique study design that efficiently controlled for selection and measurement biases by using within-patient randomization.

4.3 Methods
Study Design

The study was a prospective clinical trial comparing the efficacy of two intraoperative diagnostic imaging modalities, ICG angiography and TTF, using a within-patient randomized design. The primary objective of this study was to compare the sensitivity and specificity of indocyanine green angiography versus transit–time flowmetry to detect technical problems in coronary artery bypass grafts using x-ray coronary angiography as the reference standard. Ancillary endpoints included comparison of the positive and negative predictive values of each test.

Patient Population

Inclusion Criteria: All hemodynamically stable patients scheduled for isolated primary coronary bypass surgery were eligible. This includes both elective and urgent cases with either conventional or beating heart coronary artery bypass. Patients were eligible regardless of their coronary anatomy or the conduits used. All eligible patients were approached by the research assistant and signed a consent form approved by the institution’s Research Ethics Committee. Exclusion Criteria: Patients in cardiogenic shock were excluded. Patients with allergy to indocyanine green dye were excluded from the study. Patients with absolute or relative contraindications to study-directed x-ray contrast dye angiography were also excluded from the study. These included severe peripheral or carotid vascular disease, allergy to contrast dye, obligatory anticoagulation or renal failure with serum creatinine greater than 150 µmol/L. Pregnant women and women of child-bearing age were excluded.
Study Procedures

Randomization:

Study patients underwent intraoperative patency assessment with ICG angiography and TTF, and, reference standard x-ray coronary angiography in the early post-operative period. To reduce patient and vessel selection biases inherent to patency studies, all enrolled patients underwent intraoperative patency assessment with both ICG angiography and transit-time flowmetry. Hence, the same grafts were examined with the two modalities. To minimize bias introduced by the surgeon having knowledge of the outcome of one method of patency assessment on his/her interpretation of the other method, either ICG angiography or TTF were randomly assigned to be revealed to the surgeon first, with the opposing method being revealed second, i.e. ICG then TTF or TTF then ICG. Randomization was therefore, within patients, and not between patients. Allocation was carried out in the operating room using a randomly determined block size of four to six.

Intraoperative Patency Assessment:

ICG angiograms were performed on all grafts using the Novadaq Spy Imaging System (Novadaq Inc., Concord, Ontario, Canada). Initial work by our group has identified optimal doses of ICG dye and optimal viewing angles to perform satisfactory angiograms by this technique. (295)
Visual assessment of the intraoperative angiogram was be made by the operating surgeon and classified according to the following classification system: 1. *Normal* = widely patent, less than 50% stenosis at any location in the graft, proximal anastomosis, distal anastomosis, or immediate 1 cm of target vessel, and normal TIMI III flow characteristics; 2. *Abnormal* = patent, with > 50% stenosis at any location in graft, proximal or distal anastomosis, or immediate 1 cm of target vessel, or poor flow characteristics (non-TIMI III flow); or 3. *Occluded*.

Transit-time flowmetry was also performed on the same grafts using the Medi-Stim Butterfly Flowmeter transit-time flow measurement system (Medtronic Inc, Minneapolis, MN). An appropriate size ultrasound probe (2 mm to 4 mm) was selected for each vessel and the total volumetric flow, diastolic flow fraction and pulsatility index were measured. Measurements were taken with optimal hemodynamic conditions immediately prior to chest closure and acceptable contact between the probe and the graft (acoustic coupling index > 50%). Grafts were characterized as 1. *Normal*, 2. *Abnormal*, or 3. *Occluded*: 1. A graft was considered to be *Normal* if all three of the following transit time patency criteria were present: >50% diastolic flow fraction, a pulsatility index of less than 5 and a mean flow of greater than 10 ml/min; 2. Grafts were deemed *Abnormal* if any two of: <50% diastolic flow fraction, a pulsatility index of greater than 5, or, a mean flow less than 10 ml /min were present; 3. If there was no quantifiable flow despite repeated attempts with appropriate sized probes, a graft was deemed *Occluded*.
Intraoperative Management

Grafts believed to have significant technical error were not revised until both methods of patency assessment were performed. All grafts deemed Occluded by either technique were revised in all cases since it was deemed unethical to leave the operating room with known graft occlusions. Abnormal grafts were revised at the discretion of the operating surgeon. The basis for non-intervention for Abnormal grafts was recorded by the operating surgeon. Grafts which were revised were carefully inspected for the cause of graft failure and the findings were recorded.

Postoperative Care

Standard postoperative care was provided to all patients. All patients received 325mg aspirin daily starting 6 hours postoperatively and this was continued indefinitely. In case of aspirin intolerance or allergy, antithrombotic therapy was individualized according the patient and physician preference. All other medications were prescribed as clinically indicated. Patients with radial artery grafts were started on a postoperative regimen of intravenous nitroglycerin in the intensive care unit followed by oral nifedipine 20 mg daily starting on the first postoperative day when tolerable. (297)

X-Ray Angiography

X-ray angiography served as the reference standard to determine the sensitivity and specificity of the intraoperative imaging techniques. All eligible patients were requested to undergo post-operative X-ray angiography as part of the study protocol. Patients with new contraindications to x-ray angiography were excluded from this portion of the study as were protocol violations and patient refusals. The reason for
exclusion was recorded in all cases. Patients were transferred to the cardiac catheterization lab for standard x-ray coronary and graft angiography from the cardiovascular ward when medically stable. When logistically feasible, x-ray angiography occurred on the fourth post-operative day. All post-operative angiography was performed via the femoral artery approach. Two orthogonal angiographic views of each graft were performed. All x-ray angiograms underwent single reading by the interventional cardiologist performing the procedure, who was blinded to any intraoperative findings. All cardiologists involved in this study were experienced in reading angiograms for clinical trials.

**Endpoint Assessment**

For the reference standard x-ray angiography, grafts were classified as follows: 1. Normal if they had no stenosis >50% at any anastomosis, in the graft body or in the 1 cm of native vessel distal to the graft-coronary anastomosis; 2. Abnormal if they were patent but had stenosis >50% at any anastomosis, in the graft body or in the 1 cm of native vessel distal to the graft-coronary anastomosis; or 3. Occluded. Intraoperative classification of grafts with ICG and TTF was performed as described above. The primary study endpoint was the number of Abnormal or Occluded grafts. The primary study objective was to compare the sensitivity and specificity of each technique to identify Abnormal or Occluded grafts versus the reference standard (pathological findings at surgery or autopsy or postoperative x-ray angiography).
Sensitivity was calculated according to the usual convention, where sensitivity is equal to the ratio of true positives to the sum of true positives and false negatives. (298) Specificity was also calculated according to convention, where specificity is equal to the ratio of true negatives to the sum of true negatives and false positives.

In this study, a true positive was a graft deemed to Abnormal or Occluded by ICG angiography or TTF and also found to be Abnormal or Occluded on the reference x-ray angiogram. A true negative occurred when a graft was rated Normal by ICG angiography or TTF and also was rated Normal on reference x-ray angiography. A false positive occurred when ICG angiography or TTF identified a graft to be Abnormal or Occluded but the reference standard x-ray angiogram found the graft was Normal. A false negative occurred when ICG angiography or TTF identified a graft to be Normal but the reference standard x-ray angiogram found the graft was Abnormal or Occluded.

When a graft was revised in the operating room based in ICG angiography or TTF, the post-operative x-ray angiogram could not assess the validity of the operative finding since revision took place prior to x-ray angiogram. In these cases, the reference standard used was the pathologic analysis of the graft/anastomosis by the surgeon at the time of revision. At the time of intraoperative revision, if there were clear findings of a graft problem (i.e. purse-stringing, twisting, occlusive stitch, dissection etc.), the intraoperative patency assessment finding was deemed a true positive. If no clear pathologic evidence of a graft problem was noted during revision, the intraoperative patency assessment finding was deemed to be a false positive. For any patient who
died without undergoing postoperative angiography, autopsy findings would be used if a post mortem was performed.

**Data Management and Statistical Methods**

Case record forms regarding patient demographics were completed by the research assistant. Intra-operative data was completed by the operating surgeon and research assistant and post-operative x-ray angiography analysis was recorded by the angiographer in a blinded fashion. Data was managed in a Microsoft Access 2003 database (Microsoft Corp., Seattle, WA).

The primary comparison of the overall difference in sensitivity and specificity between the two techniques was performed using an extended McNemar test for paired data.\(^{(299)}\) The extended McNemar test allows for comparison of the difference in sensitivity and specificity of the two techniques simultaneously and avoids the problem of multiple testing (i.e. sensitivity and specificity) inherent to comparisons of diagnostic tests. Our sample size calculation, revised on the basis of a pre-specified interim analysis for safety endpoint, established that 164 grafts were needed to have 80% power to demonstrate a 40% difference in sensitivity between the two techniques assuming the prevalence of true positives was 10%. Previous studies have shown that the postoperative patency of grafts within a given patient have a 5% to 15% intra-patient correlation. To account for intra-patient correlation, a correction factor of 10% correlation was applied.\(^{(300)}\) Based on our institutional average of 3.1 grafts per patient, this meant 53 patients were needed to undergo the intraoperative studies and
post-operative x-ray angiography. Given the invasive nature of the post-operative angiogram, we anticipated that 50% of randomized patients would be either ineligible or unwilling to participate in post-operative x-ray angiography. Hence, a total of 106 patients were intended to be recruited in this study. Individual comparisons of sensitivity and specificity were performed using McNemar’s test for paired proportional data. Positive and negative predictive values were calculated according to standard methods and compared using Fisher’s Exact test.

4.4 Results

Patients

Between February 2004 and March 2005, 106 patients were enrolled. A trial summary is presented in Figure 4.1. Table 4.1 lists the baseline characteristics of the total study population and the 46 patients who underwent reference x-ray angiography. Patients who underwent reference x-ray angiography were generally representative of the total group of patients recruited. There was a non-significant trend towards better preoperative New York Heart Association (NYHA) functional status among patients undergoing x-ray angiography. No other differences between groups approached statistical significance.

Operative Data

Operative data are presented in Table 4.2. In total, 339 coronary bypass grafts were performed, of which 201 were arterial grafts. Virtually all cases were performed with cardioplegic arrest and cardiopulmonary bypass. There were no significant differences
in operative characteristics between patients enrolled and those who underwent post-operative x-ray angiography. Protocol violations occurred in six patients: four patients did not receive complete TTF assessment due to surgeon concern about damaging arterial grafts during skeletonization of a small part of the pedicle needed to make contact with the TTF ultrasound probe (six arterial grafts were not studied in these patients), and two patients were withdrawn from the study after randomization due to surgeon concern about the extra operative time required to perform the intraoperative studies.

**X-Ray Angiography**

X-ray angiography was performed in 46 of 106 enrolled patients (43.3%). In 45 patients, x-ray angiography was performed for study purposes at mean of interval of 5.8±2.4 days after bypass surgery. One patient underwent x-ray angiography at 76 days postoperatively for recurrent angina. This patient had three grafts constructed and studied intraoperatively with ICG angiography and TTF. One graft (RIMA-LAD) was revised in the operating room due to excessive bleeding and this graft was not re-imaged with ICG angiography or TTF and is therefore ineligible for the analysis. This graft was deemed to be 99% occluded at repeat angiography and angioplasty was performed. Information regarding the other two grafts is included in the primary analysis. Reasons for not undergoing angiography included protocol violations in 6 patients (as described above), postoperative medical condition precluding the performance of research angiography in 12 patients, lack of availability of cardiac catheterization laboratory in 9 patients and withdrawal of consent for the x-ray
angiogram in 33 patients. No patients experienced any complications related to study angiography.

**Primary Analysis**

In total, 139 grafts were reviewed with all three techniques. Full details of intraoperative ICG angiography and TTF assessment and reference standard assessment are presented in Table 4.3. There were 12/139 (8.6%) grafts demonstrated to be either Abnormal (7/139, 5.0%) or Occluded (5/139, 3.6%) by reference standard x-ray angiography or surgical findings. All total Occlusions occurred in saphenous vein grafts of which 5/49 (10.2%) were totally occluded. By reference standard, Abnormal grafts were observed in 3/46 (6.5%) LIMA grafts, 0/12 (0%) RIMA grafts, 2/32 (6.3%) radial artery grafts and 2/49 (4.1%) of saphenous vein grafts.

The sensitivity and specificity of ICG angiography to detect Abnormal/Occluded grafts was 83% and 100%, respectively. The sensitivity and specificity of TTF to detect Abnormal/Occluded grafts was 25% and 98.4%, respectively. The p-value for the primary endpoint of the overall comparison of sensitivity and specificity between ICG angiography and TTF was 0.011. (see Tables 4.4. and 4.5.) The difference between sensitivity for ICG angiography and TTF was 58% with a 95% confidence interval of 30% to 86%, p=0.023. The difference between specificity for ICG angiography and TTF was 1.8% with 95% confidence interval of -0.3% to 3.9%, p=0.47. The Positive Predictive Value was 100% for ICG angiography and 60% for TTF, p=0.68. The
Negative Predictive Value was 98.4% for ICG angiography and 93.2% for TTF, p=0.79.

**False Negatives:** There was one vein graft found to be totally occluded on post-operative angiography which had a normal ICG angiogram and normal TTF measurements (mean flow 56ml/min, pulsatility index 2.0, diastolic flow fraction 69%). For ICG angiography, there was one additional false negative case: a diffuse 80% narrowing of a distal radial artery graft in which the graft lumen was not well visualized intraoperatively due to a thick graft pedicle. For TTF, 8 additional false negatives occurred. These included: three Abnormal LIMA-LAD anastomoses (including one 60% lesion in the immediate distal vessel past the graft-coronary anastomosis), one Abnormal diffuse 80% distal narrowing of a radial artery graft, one Abnormal distal radial artery- obtuse marginal anastomosis, one Abnormal and two Occluded vein grafts. Representative figures are presented in Figures 2 and 3.

**False Positives:** Two grafts had abnormal TTF flows, but normal x-ray angiograms (i.e. false positives). These included a LIMA-LAD graft with mean flow of 6 ml/min and a pulsatility index of 8.9, and a diastolic flow fraction of 70%, and a radial artery to the diagonal branch with a mean flow of 14 ml/min, a pulsatility index of 7.3, and a diastolic flow fraction of 29%. Both grafts had normal x-ray angiograms with no significant stenoses and TIMI III flow. There were no false positives for ICG angiography.
Mean intraoperative TTF flow was $31.8\pm16.3$ ml/min in grafts deemed *Normal* by the reference standard, $24.4\pm8.7$ ml/min in grafts deemed *Abnormal* by the reference standard, and $16.4\pm23.0$ ml/min in grafts determined to be *Occluded* by reference standard (overall ANOVA $p =0.07$). This included two grafts with intraoperative mean flows of 0 ml/min which were both corrected at the time of operation. Mean intraoperative TTF derived pulsatility index was $2.8\pm1.4$ in grafts deemed *Normal* by x-ray angiography, $3.0\pm1.1$ in grafts deemed *Abnormal* by x-ray angiography, and $4.6 \pm 3.2$ in *Occluded grafts* (overall ANOVA $p =0.1$), including two grafts with no flow and undefined pulsatility indices. Mean intraoperative TTF derived diastolic flow fraction was $57.3\pm19.3$ in grafts deemed *Normal* by x-ray angiography, $58.4\pm8.1$ in grafts deemed *Abnormal* by x-ray angiography, and $34.0 \pm 32.3$ in *Occluded grafts* (overall ANOVA $p =0.03$).

**Clinical Outcomes**

Clinical outcomes are presented in Table 4.6. There were no significant differences in clinical outcomes between all enrolled patients and those who underwent x-ray angiography. The median post-operative length of stay was similar between groups. There were no perioperative deaths. Perioperative myocardial infarction occurred in six (5.6%) patients, including one patient with an abnormal LIMA-LAD graft. Repeat revascularization occurred in two patients. In one patient, a LIMA-LAD insertion stenosis was detected with ICG angiography but not repaired at the time of surgery. The patient underwent subsequent x-ray angiography for study purposes and the lesion was again noted. Due to subsequent anginal symptoms, angioplasty and stenting of this
anastomosis was later performed. The other patient was described above under the X-ray Angiography heading. Overall, death, myocardial infarction, or repeat revascularization occurred in 6.6% of enrolled patients. Among the 46 patients who underwent x-ray angiography, peak serum troponin was 0.24±2.4 μmol/L among patients with Normal grafts and 1.2±1.3 μmol/L among patients with Abnormal/Occluded grafts, p=0.17.

4.5 Discussion

Increasing emphasis is being placed on quality assessment in cardiac surgery. With the rise of off-pump coronary surgery, transit-time flow measurement has become a popular method to assess graft patency. Although TTF is rapid and simple to use, the technique does not produce an image and interpretation of flow data is often difficult and less intuitive than an angiographic depiction of the graft. Poor graft flow may represent an anastomotic problem, a graft body problem such as graft spasm, or disease downstream in the coronary artery. Alternatively, graft flow may be adequate but the heel or the toe of the anastomosis may be stenotic. Flow measurements are also dependant on several factors including the patient’s systemic blood pressure, the diameter of the target vessel, the size of the distal arterial bed, and residual antegrade flow in the target vessel. (301)

Indocyanine green angiography is a new technique for intraoperative graft assessment. Our early experience with ICG angiography suggested it was an effective and highly reproducible method of achieving a high quality angiographic depiction of the graft, anastomoses, and target vessel, including non-occlusive stenoses. (295)
This trial was designed to determine the superior method of verifying intraoperative graft patency. Our investigation revealed that ICG angiography had superior diagnostic accuracy versus TTF using x-ray angiography as the reference standard. In total, 12 of 139 grafts (8.6%) studied by the reference standard were abnormal or occluded in this study. ICG angiography correctly identified 83% of these abnormal/occluded grafts while TTF identified only 25%. ICG angiography correctly identified 87.5% of eight grafts with non-occlusive (>50%) stenoses while TTF was not able to identify any of these abnormal grafts. Among five grafts that were determined to be totally occluded by the reference standard, ICG angiography identified 80% while TTF identified 60%. Our observation that TTF has lower fidelity to identify abnormal (>50% stenosis) but patent grafts than totally occluded grafts confirms previous results from an observational study.(294) In off-pump cases, TTF measurements are recommended to be performed with a proximal snare in place by some authors.(296) We did not snare proximally as most cases were performed on-pump and this may technique have negatively affected the sensitivity of TTF to detect lesions.

Among the two x-ray angiographically-determined occluded grafts that were deemed normal by the TTF study, one had an abnormal ICG angiogram showing a patent but poorly functional graft in the operating room and one had a normal ICG angiogram. The overall incidence of total graft occlusion (3.6%) is at the lower end of previous angiography studies and may be reflective of increased arterial grafting use and more meticulous technique employed in patients that were expected to have post-operative angiography.
The patency characteristics of one graft appeared to have changed between the intraoperative studies and post-operative day 4 angiography. In this saphenous vein graft, both TTF flow measurement and ICG angiography showed a completely normally functioning graft which was totally occluded at the time of day 4 angiography. The cause of this occlusion was uncertain but may be due to graft kinking due to closure of the pericardium or a late graft thrombosis or embolic phenomenon. There was no biochemical or electrocardiographic evidence of post-operative myocardial infarction in this patient.

While both techniques were generally easy to use, imaging arterial grafts with thicker pedicles presents a challenge. ICG angiography and TTF both failed to recognize one radial artery graft with a diffuse spasm in its distal portion. Intraoperative vasodilator therapy with verapamil and papaverine and post-operative intravenous nitroglycerine and oral calcium channel blockade was used in this patient. We have previously demonstrated that radial artery grafts with thick pedicles are less well visualized with ICG angiography than internal mammary artery or saphenous vein grafts.(295) Adequate TTF signals of pedicled arterial grafts require partial skeletonization of the vessel to ensure good contact between the probe and the vessel wall. In four patients enrolled in this trial, the operating surgeon did not use the TTF probe due to concerns that placing it around an arterial graft would cause damage to the graft. Another emerging technology for bypass graft assessment, high frequency epicardial duplex ultrasonography, may potentially be able to adequately image the lumen of pedicled grafts without unnecessary graft manipulation - although its ease of use has not been
well characterized. It is not clear whether this graft spasm occurred during the operation or after the pharmacologic effects of the intraoperative vasodilator therapies had subsided.

The actual rate of post-operative angiography was 43.3%, lower than the anticipated 50%. This was, in part, due to the narrow window for post-operative angiography available during the patient’s hospitalization. Seven enrolled patients were willing to undergo angiography but were unable to have the procedure due to lack of cardiac catheterization laboratory time without excessive delay of patient discharge. The use a within-patient randomization prevented the detrimental effect of differential loss to follow-up.

In conclusion, indocyanine green angiography had superior diagnostic accuracy than transit-time flow measurement. This difference was observed primarily in non-occlusive but clinically significant stenoses as opposed to total occlusions. In the context of historical and contemporary graft patency studies, which have shown 4-12% of bypass grafts fail in the early postoperative period, intraoperative ICG angiography will likely be able to identify most of these lesions prior to chest closure. This potential effect on early graft patency is greater than well established methods of improving early or one-year graft patency including perioperative aspirin use and anti-lipid medications.(132;302)

Intraoperative patency assessment with indocyanine green angiography represents a significant advance in coronary bypass quality assurance.
Tables and Figures

Table 4.1. Clinical Characteristics of All Participants and Those Who Underwent X-Ray Angiography

<table>
<thead>
<tr>
<th></th>
<th>All Patients N=106</th>
<th>Patients with Angiography n=46</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – Years ± SD</td>
<td>65.5 ± 10.3</td>
<td>65.1 ± 10.1</td>
</tr>
<tr>
<td>Non-Elective Surgery – no. (%)</td>
<td>35 (33.0)</td>
<td>12 (26%)</td>
</tr>
<tr>
<td>Previous Myocardial Infarction – no. (%)</td>
<td>54 (50.9)</td>
<td>22 (47.8)</td>
</tr>
<tr>
<td>Female – no. (%)</td>
<td>14 (13.2)</td>
<td>6 (13.0)</td>
</tr>
<tr>
<td>NYHA Functional Class 3 or 4 – no. (%)</td>
<td>58 (54.7)</td>
<td>20 (43.5) †</td>
</tr>
<tr>
<td>Diabetes – no. (%)</td>
<td>35 (33.0)</td>
<td>15 (32.6)</td>
</tr>
<tr>
<td>Hypertension – no. (%)</td>
<td>66 (65.1)</td>
<td>29 (63.0)</td>
</tr>
<tr>
<td>Dyslipidemia – no. (%)</td>
<td>90 (84.9)</td>
<td>40 (87.0)</td>
</tr>
<tr>
<td>Smoking History – no. (%)</td>
<td>61 (57.5)</td>
<td>24 (52.2)</td>
</tr>
<tr>
<td>Preoperative Creatinine – no. (%)</td>
<td>87.7 ± 20.7</td>
<td>83.1 ± 17.2</td>
</tr>
<tr>
<td>Peripheral Vascular Disease – no. (%)</td>
<td>10 (9.4)</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>COPD – no. (%)</td>
<td>6 (5.7)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>LVEF &lt; 35% – no. (%)</td>
<td>19 (17.9)</td>
<td>10 (21.7)</td>
</tr>
<tr>
<td>No. of Diseased Vessels 1 / 2 / 3 – no. (%)</td>
<td>1 / 26 / 79 (0.9/24.5/74.5)</td>
<td>0 / 12 / 34 (0/26.0/74.0)</td>
</tr>
</tbody>
</table>

NYHA = New York Heart Association; COPD = Chronic Obstructive Pulmonary Disease
LVEF = estimated global left ventricular ejection fraction
† P =0.07 for comparison between all patients and those undergoing angiography.
Table 4.2. Operative Data for All Participants and Those Who Underwent X-Ray Angiography

<table>
<thead>
<tr>
<th></th>
<th>All Patients n=106</th>
<th>Patients with Angiography n=46</th>
</tr>
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<tbody>
<tr>
<td>Number of Bypass Grafts - Mean ± SD</td>
<td>3.2 ± 0.8</td>
<td>3.0 ± 0.9</td>
</tr>
<tr>
<td>Number of Arterial Grafts - Mean ± SD</td>
<td>1.9 ± 0.8</td>
<td>2.0 ± 0.7</td>
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<tr>
<td>Off-Pump – no. (%)</td>
<td>2 (1.9)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Operating Room Time - Mean ± SD</td>
<td>278.6 ± 65.4</td>
<td>282.9 ± 75.8</td>
</tr>
<tr>
<td>Cardiopulmonary Bypass Time - Mean ± SD</td>
<td>126.4 ± 34.2</td>
<td>127.9±40.7</td>
</tr>
<tr>
<td>Cross-Clamp Time - Mean ± SD</td>
<td>106.4 ± 31.1</td>
<td>107.6±35.9</td>
</tr>
<tr>
<td>TTF – no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>325 (97.6)*</td>
<td>134 (96.4)</td>
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<tr>
<td>Abnormal</td>
<td>6 (1.8)</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Occluded</td>
<td>2 (0.6)</td>
<td>2 (1.4)</td>
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<tr>
<td>ICG – no. (%)</td>
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<tr>
<td>Normal</td>
<td>328 (96.8)</td>
<td>129 (92.8)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>9 (2.6)</td>
<td>8 (5.8)</td>
</tr>
<tr>
<td>Occluded</td>
<td>2 (0.6)</td>
<td>2 (1.4)</td>
</tr>
</tbody>
</table>

* Six arterial grafts in four patients were not studied with TTF

ICG = Indocyanine green angiography    TTF = Transit-time flowmetry
Table 4.3. Graft Patency Data for ICG Angiography, TTF and Reference Standard X-Ray Angiography or Pathologic Graft Assessment Stratified by Graft Type.

<table>
<thead>
<tr>
<th></th>
<th>GRAFT TYPE</th>
<th>TOTAL</th>
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<tbody>
<tr>
<td></td>
<td>LIMA</td>
<td>RIMA</td>
</tr>
<tr>
<td>Total Grafts Reviewed</td>
<td>46</td>
<td>12</td>
</tr>
<tr>
<td>ICG Graft Assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>43</td>
<td>12</td>
</tr>
<tr>
<td>Abnormal</td>
<td>3</td>
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<tr>
<td>Occluded</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TTF Graft Assessment</td>
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<tr>
<td>Normal</td>
<td>45</td>
<td>12</td>
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<td>Abnormal</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Occluded</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reference Standard</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>43</td>
<td>12</td>
</tr>
<tr>
<td>Abnormal</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Occluded</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>True Positives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICG</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>TTF</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>False Positives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICG</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TTF</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>True Negatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICG</td>
<td>43</td>
<td>12</td>
</tr>
<tr>
<td>TTF</td>
<td>42</td>
<td>12</td>
</tr>
<tr>
<td>False Negatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICG</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TTF</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

LIMA = Left Internal Mammary Artery  RIMA = Right Internal Mammary Artery
RADIAL = Radial Artery  SVG = Saphenous Vein Graft
ICG = Indocyanine green angiography  TTF = Transit-time flowmetry
Table 4.4. Comparison of ICG angiography and TTF to detect grafts that were determined to be Occluded/Abnormal by pathologic or x-ray angiogram analysis (i.e. Sensitivity).

<table>
<thead>
<tr>
<th></th>
<th>ICG Positive</th>
<th>ICG Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTF Positive</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>TTF Negative</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>

There were 12 grafts determined to be Occluded/Abnormal by the reference standard (surgical revision or x-ray angiogram). Among the 12 Occluded/Abnormal grafts, both ICG and TTF studies successfully identified 3 graft errors, ICG identified 7 graft errors that TTF missed, and both techniques missed two graft errors.

ICG = Indocyanine green angiography  
TTF = Transit-time flowmetry
Table 4.5. Comparison of Sensitivity and Specificity of ICG Angiography and TTF

<table>
<thead>
<tr>
<th></th>
<th>ICG Angiography</th>
<th>TTF</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (TP/TP+FN)</td>
<td>10/12 (83.3%)</td>
<td>3/12 (25%)</td>
<td>0.023*</td>
</tr>
<tr>
<td>Specificity (TN/TN+FP)</td>
<td>127/127 (100%)</td>
<td>125/127 (98.4%)</td>
<td>0.47 *</td>
</tr>
<tr>
<td>Positive Predictive Value (TP/TP+FP)</td>
<td>10/10 (100%)</td>
<td>3/5 (60.0%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Negative Predictive Value (TN/TN+FN)</td>
<td>127/129 (98.4%)</td>
<td>125/134 (93.2%)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

* Overall p = 0.011 from extended McNemar Test for simultaneous comparison of sensitivity and specificity
TP = True positive   TN = True Negative
FP = False Positive  FN = False Negative
ICG = Indocyanine green angiography
TTF = Transit-time flowmetry
Table 4.6. Thirty Day Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Patients With Angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Length of Stay – Days (IQR)</td>
<td>7 (6-11)</td>
<td>7 (7-9)</td>
</tr>
<tr>
<td>Mean Length of Stay – Days ± SD</td>
<td>10.6±10.1</td>
<td>8.8 ± 5.5</td>
</tr>
<tr>
<td>Death – no. (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-fatal MI* - no. (%)</td>
<td>6 (5.6)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Peak Troponin (μmol/L) – Mean ± SD</td>
<td>0.3±2.3</td>
<td>0.4±2.1</td>
</tr>
<tr>
<td>Repeat Coronary Surgery - no. (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Coronary Angioplasty – no. (%)</td>
<td>2 (1.9)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Composite Endpoint ** - no. (%)</td>
<td>7 (6.6)</td>
<td>3 (6.5)</td>
</tr>
</tbody>
</table>

IQR – Interquartile Range  
* Myocardial Infarction (MI) = persistent new pathological Q-waves on the postoperative electrocardiogram OR characteristic ST-T segment changes with positive enzymes.  
**Composite Endpoint = Death, non-fatal MI, or any repeat revascularization;
FIGURE 4.1.

Trial Summary

106 Patients Randomized to: ICG Angio then TTF or TTF the ICG angio

46 Eligible Patients Primary Analysis Population

60 No Angiography
Protocol Violations = 6
New Contraindication for Angiography = 12
Scheduling difficulty = 9
Late Refusals = 33

45 Study X-ray Angiograms of 137 Eligible Grafts

1 Clinically Directed X-ray Angiogram of 2 Eligible Grafts
FIGURE 4.2.

Representative Transit Time Flow assessment (A), Indocyanine Green angiogram (B), and X-ray angiogram (C) images of an occluded saphenous vein graft to the posterior descending coronary artery. Transit-time flow measurements were grossly abnormal (pulsatility index >5 and diastolic flow fraction 43%). Indocyanine green angiography and x-ray angiography show an occluded vein stump (white arrows). A normally filling proximal vein graft to an obtuse marginal branch is seen in the indocyanine green angiogram (asterisk).
FIGURE 4.3.

Representative Transit Time Flow assessment (A), Indocyanine Green angiogram(B), and X-ray angiogram(C) images of a near total occlusion of a radial artery graft-first obtuse marginal branch distal anastomosis. A near total occlusion is visualized at the distal portion of the anastomosis (white arrows) on ICG and x-ray angiograms with little antegrade filling of the distal first obtuse marginal vessel. Preferential filling of a second obtuse marginal (asterisk) via the radial artery graft occurred in retrograde fashion indicating the proximal portion of the anastomosis was open. The TTF signal in this graft was normal (Flow =23 ml/min, Pulsatility Index = 4.0, 73% Diastolic Flow Fraction).
CHAPTER 5.
Intraoperative Graft Assessment Reduces Myocardial Injury after Coronary Bypass Surgery

5.1 Abstract

**Background:** Graft failure is associated with perioperative myocardial injury after coronary artery bypass grafting. The purpose of this study was to determine if intraoperative angiography to detect graft problems decreased perioperative myocardial injury rates.

**Methods:** Between January 2001 and April 2006, 2738 patients underwent coronary bypass surgery and had routine post-operative troponins measurements. 195 of these patients underwent routine intraoperative angiography with the Novadaq Spy™ fluorescence indocyanine green (ICG) angiography system to verify graft patency. Myocardial injury was defined as peak 12-48 hour postoperative level of cardiac troponin (T) in the highest quintile (≥1.3ng/mL).

**Results:** Postoperative MI occurred in 11.8% of patients undergoing intraoperative ICG angiography versus 20.0% in the control group (p= 0.005). A fully adjusted logistic regression model revealed that use of ICG angiography was strongly protective against perioperative myocardial injury (OR 0.6, 95%CI 0.4-0.9). Increasing age, preoperative creatinine, preoperative myocardial infarction, and greater coronary disease burden were independently associated with an increased risk of perioperative myocardial injury. Patients undergoing intraoperative angiography were matched to controls using propensity matching (98% match rate). Matched patients in the ICG angiography group
had significantly less perioperative myocardial injury (12.0% versus 20.3% in controls, 
p= 0.03).

**Conclusions:** Intraoperative angiography with graft revision led to significantly less 
perioperative myocardial infarctions by enzymatic criteria. This data supports the 
increasing use of intraoperative graft assessment to verify graft patency.
INTRAOPERATIVE GRAFT ASSESSMENT REDUCES MYOCARDIAL INJURY AFTER CORONARY BYPASS SURGERY

5.2 Background
Technical concerns are highly relevant in the current era as more technically demanding coronary bypass procedures including distal bypasses to small target vessels, off-pump surgery and multiple arterial grafting have become more common. Despite increasing operative complexity, coronary bypass surgery mortality has continued to decline with refinement of technique and advancement of quality assurance measures. However, coronary bypass series continue to report significant rates of early graft occlusion. Recent evidence suggests that nearly half of all major perioperative myocardial infarctions are related to early graft failure and these early graft failures have generally ascribed to technical graft problems that may be preventable with high quality intraoperative graft patency assessment.

We have previously shown that fluorescence graft angiography with indocyanine green (ICG) contrast dye was a highly sensitive method of determining intraoperative graft patency and superior to ultrasound based technologies. We found that nearly 9% of patients had graft problems of various severity identified using intraoperative imaging. The primary objective of the current study was to determine if intraoperative patency assessment with ICG angiography decreased the amount of myocardial injury during coronary bypass surgery.
5.3 Methods

Between January 2001 and April 2006, a cohort of 3661 patients underwent coronary bypass surgery and had routine post operative troponin measurements. 238 of these patients prospectively underwent routine intraoperative fluorescence ICG angiography with the Novadaq SPY® imaging system (Novadaq Technologies Inc. Mississauga, Ontario, Canada) to verify graft patency as part of various prospective studies. We compared myocardial injury in patients with and without graft patency assessment.

The primary endpoint of perioperative myocardial injury was defined according to enzymatic criteria myocardial injury was defined as peak 12–48 hour postoperative level of cardiac troponin(T) (Roche Diagnostics Canada, Laval, Quebec, Canada) in the highest decile of all 3661 patients. Based on the distribution of troponins, the primary endpoint of myocardial injury was defined as peak troponin(T) ≥2.2ng/mL. Secondary endpoints included perioperative myocardial injury defined as the highest quintile of postoperative troponins in the entire study population (>1.3ng/ml), myocardial infarction diagnosed according to the presence of new abnormal Q waves as defined by the Minnesota code criteria (307) on postoperative ECGs interpreted on a single reading by a cardiologist, death and low cardiac output syndrome (LCOS). Low cardiac output syndrome was defined according to a standardized definition: the need for postoperative intraaortic balloon pump or inotropic support for longer than 30 minutes in the intensive care unit to maintain the systolic blood pressure greater than 90 mm Hg
and the cardiac index greater than 2.2 L/min per square meter, in the presence of adequate preload and a systemic vascular resistance greater than 1200 dyn·s·cm⁻⁵.(308)

All analyses were performed with the Statistical Analysis Systems software package (SAS, Release 8.2, Cary, NC). Continuous variables are presented as mean ± standard deviation, while categorical variables are presented as either absolute counts or percentages. Categorical variables were analyzed using Fisher’s exact test. Continuous variables were analyzed by T-test. Logistic regression was used to determine independent risk factors for perioperative myocardial injury (Troponin T >2.2ng/mL). To further validate our results, patients undergoing intraoperative ICG angiography were matched 1:1 to controls using propensity matching with a validated technique.(309) Preoperative matching variables included gender, body surface area, age in years, redo surgery, ejection fraction less than 35%, urgent operation, diabetes, hypertension, peripheral vascular disease, chronic obstructive pulmonary disease, smoking, preoperative creatinine, number of bypass grafts, preoperative myocardial infarction within 30 and 5 days of operation, left main disease, and surgeon. This yielded 234 matched pairs or a 98% match rate. Comparisons of the propensity matched groups were performed using paired T-tests or McNemar’s test to account for clustering in the matched pairs.

5.4 Results

Demographic characteristics of all patients and propensity matched groups are presented in Table 5.1. In the unmatched groups, patients who did not undergo
intraoperative ICG angiography were older, had worse left ventricular ejection fraction, were less likely to be elective, had worse preoperative creatinine, had a higher prevalence of chronic renal failure (serum creatinine >150 mmol/L) and were more symptomatic. With propensity matching, all baseline differences were eliminated between groups.

Perioperative outcomes of all patients and propensity matched groups are presented in Table 5.2. Among ICG angiography patients, there were 13 perioperative graft revisions based on the imaging (5.2%). Low cardiac output syndrome occurred in more of the non-intraoperative graft assessment patients in the unmatched comparison but there was no difference between propensity matched groups. Death and perioperative myocardial infarction as defined by ECG criteria tended to be more common in the unmatched non-intraoperative graft assessment patients but outcomes were similar in the propensity matched groups. Peak postoperative troponins tended to be higher in the non-intraoperative graft assessment group. The primary endpoint of perioperative myocardial injury defined as peak troponin(T) > 2.2ng/mL occurred in 3.8% of patients undergoing intraoperative angiography versus 10.3% in the control group (Fisher’s Exact p= 0.005). A fully adjusted logistic regression model revealed that use of intraoperative ICG angiography was strongly protective against perioperative myocardial injury (Odds Ratio(OR) 0.4, 95% confidence interval(CI) 0.2-0.8) – See Table 5.3. Increasing age, preoperative creatinine, preoperative myocardial infarction and greater coronary disease burden were independently associated with an increased risk of perioperative myocardial injury (troponin(T)>2.2ng/ML). Similar results were
obtained when the more liberal highest quintile definition of troponin T >1.3ng/ml was used.(see Table 5.3) Among propensity matched patients, those in the intraoperative angiography group had significantly less perioperative myocardial injury (3.9% versus 8.8%, p=0.04) – See Table 5.2 and Figure 5.1. A logistic regression model to determine predictors of death, myocardial infarction by ECG criteria, or low cardiac output syndrome in all patients found female gender, chronic renal failure, myocardial infarction within seven days before surgery, ejection fraction < 50%, and age over 70 years at time of surgery were all significant predictors. ICG angiography was protective against death, ECG-defined myocardial infarction or low cardiac output syndrome (OR 0.75 95% CI 0.4-0.9).

5.5 Discussion

A wide variety of techniques to identify graft errors in the operating room are currently available with transit-time ultrasonic flow measurement being the most widely used, x-ray angiography being the gold standard, and ICG angiography being an emerging technology.(294;295;310-313) Our previous experiences with indocyanine green angiography suggest this technique has significantly better sensitivity for graft error detection than transit-time flowmetry without the potential risks of catheter-based contrast dye x-ray angiography and is an ideal method of graft assessment.(295;306) The main advantage of ICG angiography is its ability to detect significant(>50%) but non-occlusive stenoses and transit-time flowmetry appears to be adequate in its ability to detect total graft occlusions.(306) X-ray angiography, although the most sensitive
method of graft assessment, possesses technical and safety challenges and has not been widely adopted. The increasing implementation of ‘hybrid’ operating rooms for thoracic aortic stenting has provided new opportunities to investigate the use of x-ray angiography in coronary surgery.

In our study, we used myocardial injury defined by postoperative troponin for our primary endpoint as our sample size was not likely to be sufficient for determining the impact of ICG angiography on mortality or ECG-defined myocardial infarction. Although the role of troponin measurements in defining myocardial injury after cardiac surgery remains controversial, many authors have noted elevated troponins are strongly correlated with poorer short and long-term clinical outcomes. We believe our definition of myocardial injury as presence in the highest decile of postoperative troponin(T) (>2.2ng/mL) is highly clinically relevant. Thielmann and colleagues found that significantly elevated troponin(I) after coronary surgery was a much stronger predictor of perioperative graft failure than other biochemical markers or ECG changes.(315) Lehrke and colleagues previously found postoperative troponin(T) >0.6 ng/mL was a significant predictor of early and late mortality after coronary bypass surgery.(314)

As with any retrospective study, patient allotment into a specific therapy or intervention is associated with selection biases that cannot be fully adjusted for using multivariate methods. The patients in the intraoperative imaging group in this study were
prospectively recruited into several clinical studies and were therefore somewhat lower risk than the control group. Another significant limitation of all studies of perioperative outcomes in coronary surgery is lack of adjustment for anatomic complexity.\(316\) While we attempted to make a crude adjustment of anatomic complexity in our model by including the number of diseased vessels, we did not have specific information about quality of target vessels or completeness of revascularization.

The overall reduction of myocardial injury seen in the intraoperative imaging group in this study using this highest decile of troponin endpoint was arithmetically similar to the number of graft revisions although lack of randomization implies conclusions regarding causation are highly speculative. When considering the more liberal highest quintile of troponin endpoint, the arithmetic reduction in patients with myocardial injury was greater than the total number of graft revisions implying that patient or target vessel factors may have played a confounding role. Alternatively, the presence of intraoperative imaging technology in some cases helped surgeons to select correct target vessels and precisely identify the presence of distal lesions to identify appropriate target sites, thereby preventing myocardial injury. Although our results remained consistent with various methods of multivariate adjustment, future randomized studies with postoperative biochemical and angiographic outcomes are currently recruiting to definitively assess the role of intraoperative imaging in coronary surgery.

In summary, we demonstrate a decrease in perioperative myocardial injury with the use of intraoperative imaging to identify and correct grafts with technical errors. These
findings reinforce the growing trend towards intraoperative graft assessment as the next step in the progression of quality assurance measures that have led to substantive improvements in morbidity and mortality after coronary bypass surgery. (19) The use of intraoperative graft patency verification should be encouraged.
**Tables and Figures**

**Table 5.1** Preoperative characteristics of propensity-matched patients with troponin measurements after coronary artery bypass surgery.

<table>
<thead>
<tr>
<th></th>
<th>ALL PATIENTS</th>
<th>PROPENSITY MATCHED</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Graft Assessment</td>
<td>With ICG Angiography</td>
<td>N=238</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.7±9.9</td>
<td>63.3±9.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Female Gender</td>
<td>20%</td>
<td>15%</td>
<td>0.1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>27%</td>
<td>27%</td>
<td>1.0</td>
</tr>
<tr>
<td>EF &lt; 35%</td>
<td>22%</td>
<td>14%</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>64%</td>
<td>61%</td>
<td>0.3</td>
</tr>
<tr>
<td>Smoker</td>
<td>16%</td>
<td>11%</td>
<td>0.9</td>
</tr>
<tr>
<td>PVD</td>
<td>13%</td>
<td>11%</td>
<td>0.5</td>
</tr>
<tr>
<td>Non-Elective Operation</td>
<td>50%</td>
<td>41%</td>
<td>0.01</td>
</tr>
<tr>
<td>Preoperative creatinine (mmol/L)</td>
<td>95.3±67</td>
<td>88.3±18</td>
<td>0.001</td>
</tr>
<tr>
<td>CRF (preop Cr&gt;150)</td>
<td>3.0%</td>
<td>0%</td>
<td>0.01</td>
</tr>
<tr>
<td>COPD</td>
<td>6.5%</td>
<td>4.6%</td>
<td>0.4</td>
</tr>
<tr>
<td>CCS Class 3 or 4</td>
<td>70.0%</td>
<td>63.1%</td>
<td>0.05</td>
</tr>
<tr>
<td>MI within 30 days</td>
<td>17%</td>
<td>14%</td>
<td>0.5</td>
</tr>
<tr>
<td>MI within 7 days</td>
<td>6.9%</td>
<td>3.7%</td>
<td>0.08</td>
</tr>
</tbody>
</table>

EF = Left ventricular ejection fraction  
PVD = peripheral vascular disease  
CRF = Chronic renal failure (serum creatinine > 150 mmol/L)  
COPD = Chronic obstructive pulmonary disease  
NYHA Class = New York Heart Association Class  
MI = Myocardial infarction
Table 5.2. Perioperative characteristics of all patients with troponin measurements after coronary artery bypass surgery.

<table>
<thead>
<tr>
<th></th>
<th>ALL PATIENTS</th>
<th>PROPENSITY MATCHED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Graft Assessment N=3423</td>
<td>With ICG Angiography N=238</td>
</tr>
<tr>
<td>Clamp Time (min)</td>
<td>89.7±27</td>
<td>97.5±27</td>
</tr>
<tr>
<td>Pump Time (min)</td>
<td>108±32</td>
<td>115±33</td>
</tr>
<tr>
<td>No. of Bypass Grafts</td>
<td>3.1±0.8</td>
<td>3.1±0.8</td>
</tr>
<tr>
<td>Off-Pump</td>
<td>4.6%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Graft Revisions</td>
<td>0%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Low Cardiac Output Syndrome</td>
<td>18.4%</td>
<td>13.3%</td>
</tr>
<tr>
<td>Death</td>
<td>2.2%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Non-fatal MI **</td>
<td>3.7%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Death or Non-Fatal MI **</td>
<td>5.9%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Peak CK (U/L)</td>
<td>639±563</td>
<td>557±444</td>
</tr>
<tr>
<td>Peak Troponin(T)(ng/mL)</td>
<td>0.95±1.5</td>
<td>0.72±0.7</td>
</tr>
<tr>
<td>Troponin(T)&gt;1.3 ng/mL</td>
<td>21.0%</td>
<td>11.8%</td>
</tr>
<tr>
<td>Troponin(T)&gt;2.2 ng/mL</td>
<td>10.3%</td>
<td>3.8%</td>
</tr>
</tbody>
</table>
* Revisions based on intraoperative graft imaging on a per-patient basis
** MI = myocardial infarction defined by electrocardiographic changes
Table 5.3. Multivariate predictors of myocardial injury (troponin(T)>2.2ng/mL) and Composite endpoint of Death/MI/Low output syndrome as determined by logistic regression.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Troponin(T)&gt;2.2ng/mL</th>
<th>COMPOSITE DEATH/MI/LOS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>ICG Angiogram</td>
<td>0.4</td>
<td>(0.2 - 0.8)</td>
</tr>
<tr>
<td>Female Gender</td>
<td>1.1</td>
<td>(0.9-1.3)</td>
</tr>
<tr>
<td>Body Surface Area</td>
<td>0.6</td>
<td>(0.4-1.0)</td>
</tr>
<tr>
<td>Age &gt;70 years</td>
<td>1.0</td>
<td>(0.8-1.2)</td>
</tr>
<tr>
<td>Redo Surgery</td>
<td>1.8</td>
<td>(0.8-3.8)</td>
</tr>
<tr>
<td>Ejection Fraction &lt;50%</td>
<td>1.2</td>
<td>(1.0-1.4)</td>
</tr>
<tr>
<td>Non-elective Operation</td>
<td>0.9</td>
<td>(0.7-1.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.9</td>
<td>(0.7-1.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.1</td>
<td>(0.9-1.3)</td>
</tr>
<tr>
<td>Peripheral Vas. Disease</td>
<td>0.9</td>
<td>(0.7-1.2)</td>
</tr>
<tr>
<td>COPD</td>
<td>0.9</td>
<td>(0.8 – 1.4)</td>
</tr>
<tr>
<td>Smoker</td>
<td>1.0</td>
<td>(0.7 – 1.2)</td>
</tr>
<tr>
<td>Pre-operative Creatinine &gt;150</td>
<td>2.8</td>
<td>(1.9 - 4.2)</td>
</tr>
<tr>
<td>No. of Bypass Grafts</td>
<td>1.3</td>
<td>(1.2 – 1.5)</td>
</tr>
<tr>
<td>Preoperative MI &lt;7 days</td>
<td>2.2</td>
<td>(1.5 – 3.2)</td>
</tr>
</tbody>
</table>

EF = Left ventricular ejection fraction
PVD = peripheral vascular disease
COPD = Chronic obstructive pulmonary disease
MI = Myocardial infarction
* Revisions based on intraoperative graft imaging on a per-patient basis
** MI = myocardial infarction defined by electrocardiographic changes
Figure 5.1
Prevalence of myocardial injury after coronary bypass surgery in propensity-matched groups

* p < 0.05
CHAPTER 6.
A Randomized Comparison of Radial Artery and Saphenous Vein Coronary Bypass Grafts

6.1 Abstract

**Background:** The radial artery has been used frequently in the past decade for coronary bypass surgery despite concerns regarding radial artery patency due to graft spasm. Graft patency is a key predictor of long-term survival. We therefore sought to determine the relative patency of radial artery (RA) and saphenous vein (SV) grafts in a unique randomized controlled trial that controlled for patient and vessel selection biases.

**Methods:** Between November 1996 and January 2001, 561 patients requiring bypass surgery for triple vessel disease were enrolled at 13 centres (12 Canadian, 1 New Zealand). The left internal thoracic artery was used to bypass the anterior circulation. The target for the radial artery graft was randomly assigned as the major vessel in either the inferior (right coronary) territory or the lateral (circumflex) territory, with the saphenous vein graft used for the territory not assigned to the radial artery graft. The primary endpoint was graft occlusion determined by angiography 8-12 months postoperatively.

**Results:** Post-operative angiography was performed in 440 patients. Complete graft occlusion was present in 8.2% of radial artery grafts and 13.6% of saphenous vein grafts (p=0.009). Functional occlusion, defined as the absence of TIMI III flow,
occurred in 12.5% of radial artery grafts and 14.1% of saphenous vein grafts (p=0.37). The absence of a severe native vessel stenosis was associated with an increased risk of radial artery graft occlusion. Angiographic string sign was present in 7.0% of radial artery grafts and only 0.9% of saphenous veins, p=0.001. Harvesting of the radial artery was well tolerated. One-year freedom from cardiac death, non-fatal myocardial infarction or repeat revascularization was 88.4%. Cardiac death occurred in 5 patients (0.9%) within 1 year of surgery.

**Conclusions:** As a coronary bypass conduit, the radial artery is associated with less graft occlusion at one year than the saphenous vein. Because radial artery patency appears to depend on the severity of native vessel stenosis, it should be used only in the presence of high-grade lesions.
A RANDOMIZED COMPARISON OF RADIAL ARTERY AND SAPHENOUS VEN CORONARY BYPASS GRAFTS

6.2 Background

The radial artery was first introduced as a coronary artery bypass graft by Carpentier in 1971. Initial failures of radial artery bypass conduits suggested they were prone to perioperative graft spasm and subsequent functional occlusion. Medical therapy to prevent graft spasm with calcium channel blockers and improved graft harvesting techniques have revitalized the use of the radial artery as an additional arterial conduit. Advantages of the radial artery include ease of harvesting from the forearm, a low propensity for wound infection at the harvest site, a larger luminal diameter than other arterial grafts, and a thick, muscular wall that allows for simplified anastomosis construction.

In an attempt to evaluate the potential role of the radial artery as a bypass conduit in a rigorous manner, we initiated a randomized trial to determine whether the 8-12 month patency of the radial artery exceeds that of the saphenous vein graft using a unique study design which controls for patient and vessel selection biases.

6.3. Methods

Study Design
Patients received both a radial artery and a saphenous vein graft randomly allocated to two different coronary territories. This controlled for patient and vessel selection biases that otherwise confound comparisons. The primary study objective was to determine the angiographic patency of radial artery grafts compared with saphenous vein grafts at 8 to 12 months following surgery.

**Patient Population**

Inclusion Criteria

Patients aged less than 75 years undergoing non-emergent primary isolated coronary bypass surgery with graftable triple vessel disease and an estimated left ventricular ejection fraction greater than 35% were eligible for the study. The upper age limit was amended to include patients up to 80 years of age during the first year of the study to increase recruitment. The target coronary vessels were the left circumflex and the right coronary arteries. By protocol, they had proximal lesions with at least 70% diameter narrowing, were greater than or equal to 1.5 mm in diameter and were deemed to be acceptable quality according to visual assessment of the angiogram by the operating surgeon. Patients with a dominant circumflex coronary artery were eligible if they had sequential high grade lesions in the circumflex and suitable obtuse marginal and posterior descending branches. Arterial Dopplers of the upper extremity were required initially. However, the protocol was later amended such that they were recommended only for patients with evidence of peripheral or cerebrovascular disease.
Exclusion Criteria

Patients with non-palpable ulnar arteries or a positive Allen’s test, an abnormal upper extremity Doppler study or ultrasound, or a history of vasculitis or Raynaud’s syndrome were ineligible. Patients with bilateral varicose veins and/or stripping were ineligible. Patients with any of the following conditions that would preclude follow-up research angiography on an ethical basis were excluded: creatinine greater than 180 μmol/L, severe peripheral vascular disease, coagulopathy or obligatory use of anticoagulants, known allergy to radiographic contrast media, pregnancy, other severe co-morbid illness precluding the use of follow-up angiography, or geographic inaccessibility.

Study Protocol

Randomization

The patients signed a consent form approved by the Research Ethics Committee at each participating centre. Randomization was carried out after arrival of the patient to the operating room using a sealed envelope method stratified by site with a randomly determined block size of 4 to 6. Patients were randomly assigned to one of two graft strategies: 1) The radial artery was used to graft the circumflex territory and a saphenous vein graft was used for the right coronary system; or, 2) the radial artery was directed to the right coronary territory and a saphenous vein graft was used for the circumflex system. Since each study patient received both the study radial graft and a
control saphenous vein graft, the patients served as their own controls. Randomization was thus performed within rather than between patients.

By protocol, the study radial artery and the study vein graft were used to bypass the major branch of each target vessel on the lateral and inferior walls. The protocol strongly recommended that the internal thoracic artery be used for the left anterior descending artery distribution. Additional grafts, regardless of conduit used, were constructed as necessary and considered ancillary. Only the study radial artery and the study saphenous vein graft were used to determine the primary endpoint. The non-dominant arm was used exclusively for radial artery harvesting. Details of the surgical technique have been previously published. (297) The free radial artery pedicle was dilated in situ by a slow intraluminal injection of 4-5 ml of a dilute solution of verapamil and papaverine (5 mg verapamil and 65 mg of papaverine in 16 ml of lactated Ringer’s solution). In general, single rather than sequential grafts were constructed.

Postoperative Management and Follow-up

Patients were given aspirin 325 mg daily starting within six hours post-operatively and continued indefinitely. By protocol, patients received intravenous nitroglycerin 1-10 µg/kg/minute during the first 24 hours postoperatively in the intensive care unit. Vasoconstrictor agents such as norepinephrine and neosynephrine were generally avoided. Oral nifedipine was initiated the first postoperative day and continued for six months post-operatively. For patients intolerant to nifedipine, diltiazem or amlodipine
were substituted. Serial electrocardiograms were obtained preoperatively and at day 1 and 5 postoperatively. Patients were interviewed by telephone by the study nurse at one month, three months, six months and yearly thereafter. In-patient records were obtained for patients who had been admitted to hospital. Events of interest were recurrent angina, myocardial infarction, symptom directed angiography, percutaneous coronary angioplasty, repeat surgery and mortality. All patients were questioned regarding function of the arm (six questions) or hand (12 questions) using a modification of the Disability of the Arm, Shoulder and Hand questionnaire. (318) Scores could range from 0-24 for the arm and 0-48 for the hand. A score of \(\geq 12\) for the arm and \(\geq 18\) for the hand represented a significant limitation.

Follow-up Angiography

Patients were scheduled to undergo follow-up angiography 8 to 12 months following surgery. The window for follow-up angiography was increased to facilitate scheduling. The angiogram was not performed if any of the conditions listed as pre-operative exclusions developed in the postoperative period. Angiograms were generally performed on an outpatient basis. Nitroglycerin was injected into each graft prior to filming. At least two orthogonal views of each graft were obtained and continued exposure was used as required to visualize the distal runoff, and the size of the target bed. Injection of the native vessels, non-study grafts and aortography were not required by the protocol.
Study End Points

The primary end point of the study was the proportion of radial artery and study saphenous vein grafts completely occluded with no opacification of the target coronary vessel (i.e. Thrombolysis in Myocardial Infarction (TIMI) 0 flow) at follow-up angiography.(319) Secondary angiographic end points included perfect graft patency (TIMI III flow), presence of obstructive disease, presence of angiographic string signs, and presence of catheter tip spasm during angiography.

Secondary clinical end points included all-cause mortality, perioperative myocardial infarction (MI), late MI, re-operative cardiac surgery, and coronary angioplasty. Stroke was defined as a persistent neurological deficit at the time of death or discharge. Complications related to harvesting of the radial artery included hand claudication and thenar paraesthesia were reported according to the diagnoses specified by a consultant neurologist.

The angiographic committee consisted of four cardiologists experienced with angiography. Postoperative angiograms were adjudicated in an independent, blinded fashion by two of the four committee members with a third review in the case of disagreement. A random sample of 20% of the diagnostic angiograms were reviewed at the core laboratory to determine if angiographic inclusion and exclusion criteria were met.
Perioperative myocardial infarction was diagnosed when persistent new pathological Q-waves were present on the postoperative ECG. A late myocardial infarction was diagnosed for patients with new Q-wave or typical ST-T wave changes without Q-waves. Cause specific mortality was determined where possible from hospital records and autopsy information.

**Data Management and Statistical Analysis**

Case record forms were completed by the local research assistant and entered locally into an internet-based connection into a secured database maintained at the coordinating centre. The data were re-entered at the co-ordinating centre to identify data entry errors. Graft occlusion results for the two principal grafts in the study are reported as proportions. The primary comparison between the rates of occlusion of the radial artery and saphenous vein graft was performed on an intent-to-treat basis using McNemar’s test for paired proportional data. Statistical significance was inferred at p<0.048, to achieve an overall level of 0.05 following adjustment for a single interim analysis.

A sample size of 464 patients provided 80% power for a two-tailed test, alpha=0.05 for a 40% relative reduction in the rate of graft occlusion from an estimated 12% in the saphenous vein to 7.2% in the radial artery, assuming a 20% within patient correlation for graft occlusion. The sample size was increased to 561 patients to allow for lack of follow-up angiography in approximately 20% of patients. There was no sample size projection for secondary endpoints.
6.4 Results

Patients

The demographic and angiographic characteristics of the total study population of 561 patients and the patients who underwent postoperative angiography are listed in Table 6.1. The preoperative characteristics of patients who underwent study angiography were representative of the entire population of enrolled patients. Since each patient served as their own control, patient-related factors were controlled for by the study design. The patients were generally young and the proportion of females was low, as is typical for arterial revascularization patients in the study centres. Peripheral vascular disease was uncommon as per protocol. Preoperative medication use included aspirin (83.2%), beta-blockers (74.7%), long-acting nitrates (44.9%), ACE inhibitors (24.8%), and lipid-lowering drugs (48.7%). Preoperative diuretics (7.6%), digoxin (1.1%) or other anti-arrhythmics (0.9%) were uncommon. Intravenous heparin was used preoperatively in 17.6% of patients and intravenous nitrates were used in 3.2% of patients. Severity of target coronary vessel stenosis was similar between the radial arteries and saphenous veins, indicating the randomization was balanced.

Operative Data

Operative data is presented in Table 6.2. The study dose of verapamil/papaverine was delivered into 92.3% of study radial artery grafts. Proximal anastomosis was performed to the aorta in 98.4% of radials and 99.6% of vein grafts. Six radial arteries were proximally grafted to saphenous vein graft hoods, one was proximally grafted to the left internal thoracic artery (Y-graft) and two were proximally grafted to the study
saphenous vein graft (Y-graft). Two study vein grafts were proximally grafted to other non-study grafts.

Protocol violations (i.e. one or both study grafts not placed) occurred in 17 patients. The reason for protocol violations were: ungraftable coronary arteries (4 patients), poor radial quality or length (6 patients), poor vein quality (2 patients), right internal thoracic artery grafted to the right coronary (1 patient), radial artery grafted to the LAD (1 patient), surgeon used off-pump surgery (1 patient), patient instability prior to cardiopulmonary bypass (1 patient), and family withdrew consent (1 patient). Patients who were protocol violations were pre-specified to be ineligible for inclusion in the primary analysis.

There were 24 crossovers, i.e. a patient who received both radial artery and study saphenous vein grafts but to the territory opposite to that allocated by randomization. The reasons for crossover were inadvertent surgeon error in 19 patients and concerns about radial size or quality in 5 patients. These patients were eligible for follow-up angiography but were analyzed according to the intent-to-treat rather than treatment received for the primary endpoint.

**Post-Operative Management**

The majority of patients (94.1%) were discharged on calcium channel blockers, which were continued for three to six months in 90.0% of patients. Other discharge medications included aspirin in 92.3%, other antithrombotic medications in 8.7%, lipid-
lowering drugs in 66.7%, angiotensin converting enzyme (ACE) inhibitors in 11.3%, and beta-blockers in 70.6% of patients. Concurrent medical care at 12 months postoperatively included lipid-lowering drugs in 64.9%, ACE inhibitors in 16.2%, beta-blockers 57.1%, aspirin in 91.9%, and other antithrombotic medications in 5.0% of patients.

One-Year Angiography

Of 561 randomized patients, 440 eligible patients underwent postoperative angiography. (See Figure 6.1.) Protocol violations occurred in 17 patients and new postoperative conditions precluding a research angiogram occurred in 19 patients. Late refusals occurred in 77 patients. Angiography was not performed in any of the eight postoperative deaths. Among protocol violations, one patient who received a radial graft to the left anterior descending coronary artery due to an unusable left internal thoracic artery requested and received study angiography. However, these results (all grafts patent) are not included in the primary analysis since the radial artery was not placed to a study-sanctioned target vessel. Of the 440 eligible patients who underwent postoperative angiography, 431 patients underwent study angiography at 10.9 +/- 4.3 months postoperatively (range 3.5 to 46.8 months). Nine patients had clinically directed angiograms performed at 4.7 +/- 2.4 months following surgery (range 3 weeks to 9 months). Post-mortem information was obtained in one patient who did not have angiography (all grafts patent).
Primary Analysis

The primary endpoint of complete graft occlusion occurred in 13.6% (60/440) of study saphenous vein grafts versus 8.2% (36/440) of radial artery grafts (McNemar p=0.009) using intent-to-treat analysis. (See Table 6.3.) Complete graft occlusion occurred in 13.9% (61/440) of veins compared with 8.0% (35/440) of radial artery grafts (p=0.005) using treatment received analysis. Radial artery graft patency was highly dependent on the severity of the proximal coronary lesion, where 5.9% (16/271) of radial artery grafts were totally occluded if the preoperative target vessel stenosis was greater than 90% and 11.8% (20/169) of radial grafts were completely occluded if native vessel stenosis was less than 90%, p=0.03. All occluded radial arteries were proximally anastomosed directly to the aorta. In saphenous veins, total occlusion occurred in 12.2% (35/286) of veins grafted to target vessels with greater than 90% proximal stenosis and 16.2% (25/154) of veins grafted to target vessels with less than 90% proximal stenosis, p=0.24. Within-patient correlation between study grafts for the primary endpoint was 2.6%.

String sign, defined as a diffusely narrowed graft with a diameter of less than 1 mm and at least TIMI I flow, was present in 7.0% (31/440) of radial artery grafts and only 0.9% (4/440) of saphenous veins, p = 0.001. The presence of radial artery string sign was also highly dependent on severity of proximal native vessel stenosis, where radial artery string sign occurred in 3.7% of radial arteries grafted to target coronaries with greater than 90% proximal stenosis and in 12.4% of radial arteries grafted to target coronaries with less than 90% proximal stenosis, p= 0.0005. Catheter tip graft spasm at the time
of follow-up angiography was unusual with saphenous veins 2.5% (11/440) whereas catheter tip graft spasm was present in 10.3% (50/440) of radial artery grafts. Absence of TIMI III flow occurred in 14.3% of saphenous vein grafts (63/440 grafts) and 12.3% of radial artery grafts (54/440 grafts) according to the intent-to-treat analysis, p=0.37.

Patency of either radial artery or saphenous vein grafts did not depend upon the bypassed native vessel. Total occlusion occurred in the right coronary artery territory in 4.3% (19/221) and 6.8% (30/219) of radial artery and saphenous vein grafts, respectively, and occurred in the left circumflex artery territory in 3.9% (17/219) and 6.8% (30/221) of radial artery and saphenous vein grafts, respectively.

**Patient Safety**

Radial harvest site infection requiring readmission was reported in 1 patient (0.2%). The six month mean hand function score was 6.4 ± 1.2 units, range 6 to 17, and mean arm function score was 6.3 ± 1.2 units, range 6 to 19. One patient (0.2%) had a hand score greater than 18. Thirty-two (6%) patients reported moderate to severe symptoms of thenar paresthesia or numbness at one month and this decreased to 6 patients (1%) at 12 month follow-up. Ten patients (2%) reported moderate to severe hand weakness at one month and this decreased to 5 patients (1%) at 12 month follow-up. No patient report hand claudication or ischemia. There were no reports of adverse patient events occurring during follow-up angiography.
**Clinical End-Points**

Intra-aortic balloon pump insertion was necessary in five patients (0.9%) perioperatively. Early chest re-exploration for bleeding occurred in 15 patients (2.7%), cardiogenic shock occurred in two patients (0.4%) and cardiac tamponade occurred in one patient (0.2%). Two patients (0.4%) required late chest re-exploration for cardiogenic shock and two patients (0.4%) required late chest re-opening for cardiac tamponade. No patients required sternal debridement or re-wiring for infection.

Thirty day and one year clinical outcomes are listed in Table 6.4. No patients were lost to one-year follow-up. One-year survival was 98.6% (553/561 patients). There were four perioperative deaths and four post-discharge deaths in the first year of follow-up. Five of the deaths in the first year following surgery were due to cardiac causes (3 perioperative deaths, 2 late deaths). Cerebrovascular accident caused one perioperative death. One late death was attributable to cancer and one late death was attributable to massive pulmonary embolus following an unrelated peripheral vascular procedure more than six months postoperatively. Non-fatal myocardial infarction (MI) occurred in 9.8% (55/561) of patients perioperatively. Non-fatal MI occurred in the territory of the radial artery in 3.2% (18/561) of patients, in the territory of the study saphenous vein graft in 3.0% (17/561) of patients, in the left internal mammary artery graft territory in 2.8% (16/561) of patients, and location was indeterminate in 0.7% (4/561) of patients. In one-year follow-up, one patient (0.1%) experienced non-fatal myocardial infarction post discharge.
No patients required repeat cardiac surgery during one-year follow-up. Four patients underwent clinically directed post-discharge percutaneous coronary angioplasty. Angioplasties were performed to two study saphenous vein grafts, to one native coronary artery beyond a study saphenous vein distal anastomosis and to one study radial artery at the proximal anastomosis. Overall one-year freedom from cardiac death, non-fatal myocardial infarction or repeat revascularization was in this study was 88.4% (496/561 patients).

6.5 Discussion

Patency of the radial artery coronary bypass graft was superior to the usual saphenous vein graft at one-year in this randomized multicentre clinical trial. The primary endpoint of graft occlusion was significantly less common in radial arteries (8.2%) than saphenous vein grafts (13.6%), p=0.009. This corresponds to an absolute difference in graft occlusions of 5.4% (95% confidence interval 5.0% to 5.8%) and a relative risk reduction for graft occlusion of 39.7% (95% confidence interval 27.9% to 51.5%) favouring of the radial artery. Previous studies have established the superiority of the left internal thoracic artery over saphenous vein grafts for left anterior descending coronary artery revascularization.(138) This study is the first large randomized controlled trial to establish that a second arterial conduit provides improved patency over the saphenous vein.

The study design was unique in that the patient received both the study radial artery graft and the control saphenous vein graft. By enabling each patient to serve as their
own control, inherent biases regarding patient selection were avoided. Additionally, since the radial artery and saphenous vein grafts were randomized within each patient, the effect of target vessel location was also controlled and could be analysed independently. Grafting to either the left circumflex coronary or right coronary territory did not influence graft patency in this study. Moreover, although the design vitiated inter-group differences, the groups undergoing radial artery grafting to either territory were similar to each other and clinical outcomes were predictably similar. Thus, we were able to focus on the primary endpoint without concern about confounding or differential loss to follow-up.

This study was designed to specifically place the radial artery in high demand situations by stipulating the proximal target vessel stenosis was greater than 70%. Despite this deliberate inclusion criterion, a gradient in radial graft performance was still evident, with poorer radial artery patency observed when grafted to less severe target lesions. The relationship between severity of proximal native vessel stenosis and arterial graft patency has been previously reported for internal thoracic, gastroepiploic and radial artery grafts in retrospective studies. In these studies, the patency rate of arterial grafts that were not grafted to the left anterior descending coronary artery improved substantially as severity of proximal stenosis increased from 70 to 90% but generally did not further improve beyond 90%. The mechanism of failure in these grafts is likely competitive flow from the native coronary vessel. Characteristics of the radial artery including increased wall thickness, density, and organization of myocytes may increase the propensity for graft spasm in this artery, particularly as a consequence...
of competitive flow. (321) The increased reactivity of radial artery grafts was also noted in the increased rate of catheter-tip spasm (11.3% radials vs. 2.5% veins) despite high compliance with calcium channel blocker therapy for the first six months. The cut-off point of 90% target vessel stenosis should be interpreted with some caution as the severity of the target stenosis was derived from single observer visual assessment and not quantitative angiography. Since visual assessment tends to overestimate the severity of stenosis in comparison to quantitative angiography, less severe lesions may still benefit from radial artery grafting. (322)

Competitive flow was also significantly related to the development of radial artery graft spasm or angiographic string signs. The clinical significance of radial artery string signs has not been established. Royse and colleagues reported that among 14 string signs observed in postoperative angiography of 129 radial arteries, only 2 demonstrated reversible ischemia in the radial-grafted territory by stress perfusion scanning. (323) Using the more stringent definition of perfect patency (i.e. TIMI III flow), graft occlusion occurred in 12.3% of radial artery grafts and 14.3% of saphenous vein grafts. Among 18 radial artery grafts that were imperfectly patent (TIMI I or II flow), ten (56%) were grafted to native vessels with less than 90% stenosis. Possati and colleagues have shown that these grafts may potentially become perfectly patent at late follow-up. (204)

Radial artery harvest was generally well tolerated by study patients and complications were rare in this study. There were no hand or arm ischemic complications, 0.2% incidence of wound infection requiring readmission to hospital, and 6% incidence of
paresthesia or numbness at one month declining to 1% at one year. By comparison, a previous report of 3977 radial harvests for CABG reported no arm or hand ischemic symptoms, early or late wound infection in 0.4% of patients, and numbness or paresthesia in 9.5% of patients at 3 month follow-up. (238) Although this study dictated that radial arteries were harvested only from the non-dominant arm, the low rate of arm and hand complications suggest that harvest from the dominant hand is likely safe in patients with limited conduit availability.

Freedom from myocardial infarction, repeat revascularization, or death at one year was 88.4% in this multicentre trial. This compares favourably to two recent multicentre randomized trials comparing coronary bypass surgery to percutaneous coronary stenting, the Arterial Revascularization Therapies Study (ARTS) and the Stent or Surgery (SoS) trial, which had overall event-free survivals of 87.8% and 87.0% at one year, respectively in their surgical patients. (324;325) The incidence of repeat coronary revascularization at one year in the current study was 0.7% compared with 0.7% in the ARTS trial and 3% in the SoS trial surgical patients.

The incidence of vein graft occlusion at one-year in this study was 13.6%. Previous studies of saphenous vein graft patency have shown one-year patency between 85% and 90%. (See Table 1.1) Given the natural history of accelerated atherosclerosis in vein grafts, the superiority of radial artery conduits over vein grafts may be even greater at 5 and 10 year follow-up.
Although the study was designed to include patients at lower risk for radial artery atherosclerosis, inadequate size or quality of the radial artery precluded its use in six patients. In an additional five patients, concerns about radial artery size or quality caused the operating surgeon to deviate from the randomized target vessel. The incidence of inadequate radial artery due to atherosclerotic changes would likely be higher in the general coronary bypass population and particularly in patients with severe peripheral vascular disease.

In conclusion, radial artery graft patency was superior to saphenous vein graft patency at one year when careful harvesting technique and strict adherence to post-operative calcium channel blockers was employed. Surgeons can confidently use the radial artery as a second arterial bypass graft, particularly in patients with severe native vessel stenosis. A five-year angiographic follow-up study of the current trial patients is currently underway.
Table 6.1. Clinical Characteristics of all Participants and those undergoing Angiography

<table>
<thead>
<tr>
<th></th>
<th>All Patients n=561</th>
<th>Patients with Angiography n=440</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.0 ± 8.5</td>
<td>60.8 ± 8.4</td>
</tr>
<tr>
<td>Age &gt; 70 years</td>
<td>111 (19.8%)</td>
<td>61 (13.9%)</td>
</tr>
<tr>
<td>Non-Elective Surgery</td>
<td>196 (34.9%)</td>
<td>145 (33.0%)</td>
</tr>
<tr>
<td>Previous Myocardial Infarction</td>
<td>264 (47.1%)</td>
<td>204 (46.4%)</td>
</tr>
<tr>
<td>Female</td>
<td>75 (13.4%)</td>
<td>57 (12.9%)</td>
</tr>
<tr>
<td>CCS Class 1/2/3/4 *</td>
<td>9/ 133 /267 /152 (1.6 / 23.7 / 47.6 / 27.1%)</td>
<td>7 / 108 / 218 / 107 (1.6 / 24.5 / 49.6 / 24.3%)</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>18 (3.2%)</td>
<td>12 (2.7%)</td>
</tr>
<tr>
<td>Diabetes oral/insulin</td>
<td>114/34 (20.3/6.1%)</td>
<td>93/22 (21.1/5.0%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>271 (48.3%)</td>
<td>203 (46.1%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>375 (67.0%)</td>
<td>303 (69.0%)</td>
</tr>
<tr>
<td>Current Smoking</td>
<td>104 (18.5%)</td>
<td>76 (17.3%)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>93.0 ± 20.1</td>
<td>92.7 ± 19.9</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>50 (8.9%)</td>
<td>32 (7.3%)</td>
</tr>
<tr>
<td>LV Grade 1 / 2 / 3 or 4 †</td>
<td>272/280/9 (48.2/50.1/1.5%)</td>
<td>213 / 220 / 7 (48.4 / 50.0 / 1.6%)</td>
</tr>
<tr>
<td>Left Main Stenosis &gt;50%</td>
<td>49 (8.7%)</td>
<td>42 (9.5%)</td>
</tr>
<tr>
<td>Right Coronary Stenosis 70-89%/90-99%/100%</td>
<td>172 / 161 / 228 (30.7/28.7/40.6%)</td>
<td>135 / 129 / 176 (30.7/29.3/40.0%)</td>
</tr>
<tr>
<td>Circumflex Stenosis 70-89%/90-99%/100%</td>
<td>247 / 200 / 114 (44.0/35.7/20.3%)</td>
<td>188 / 153 / 99 (42.7/34.8/22.5%)</td>
</tr>
<tr>
<td>Radial Artery Target Vessel Stenosis</td>
<td>222 / 174 / 165 (39.6 / 31.0 / 29.4%)</td>
<td>169 / 135 / 136 (38.7 / 30.7 / 30.9%)</td>
</tr>
<tr>
<td>Saphenous Vein Target Vessel Stenosis</td>
<td>197 / 187 / 177 (35.1 / 33.3 / 31.6%)</td>
<td>154 / 147 / 139 (35.0 / 33.4 / 31.6%)</td>
</tr>
</tbody>
</table>

* Canadian Cardiovascular Society Angina Class
† Estimated global left ventricular ejection fraction (LVEF): 1 = LVEF > 50%; 2 = LVEF 35-49%; 3 = LVEF 20-34%; 4 = LVEF < 20%
Table 6.2. Operative Data for All Patients and Those Undergoing Angiography

<table>
<thead>
<tr>
<th></th>
<th>All Patients n=561</th>
<th>Patients with Angiography n=440</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Distal Anastomoses</td>
<td>3.8 ± 0.7</td>
<td>3.8 ± 0.7</td>
</tr>
<tr>
<td>Proximal Aortic Anastomosis</td>
<td>552 (98.4%)</td>
<td>433 (98.4%)</td>
</tr>
<tr>
<td>Blood Cardioplegia</td>
<td>467 (83.2%)</td>
<td>365 (83.0%)</td>
</tr>
<tr>
<td>Study Papaverine Dose Delivered</td>
<td>518 (92.3%)</td>
<td>407 (92.5%)</td>
</tr>
<tr>
<td>Operating Room Time</td>
<td>234 ± 58 min</td>
<td>233 ± 55 min</td>
</tr>
<tr>
<td>Cardiopulmonary Bypass Time</td>
<td>97 ± 26 min</td>
<td>97 ± 26 min</td>
</tr>
<tr>
<td>Cross-Clamp Time</td>
<td>73 ± 26 min</td>
<td>74 ± 25 min</td>
</tr>
<tr>
<td>Antifibrinolytic Use</td>
<td>100 (17.8%)</td>
<td>79 (18.0%)</td>
</tr>
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</table>
Table 6.3. Angiographic Endpoints Among Patients in the Radial Artery Patency Study
(n=440)

<table>
<thead>
<tr>
<th></th>
<th>Radial Artery, n (%)</th>
<th>Saphenous Vein, n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft Occlusion (TIMI 0)</td>
<td>36 (8.2%)</td>
<td>60 (13.6%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Graft Occlusion (TIMI 0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 90% Native Vessel Stenosis</td>
<td>20/169 (11.8%)†</td>
<td>25/154 (16.2%)‡</td>
<td>† 0.03</td>
</tr>
<tr>
<td>&gt; 90% Native Vessel Stenosis</td>
<td>16/271 (5.9%)†</td>
<td>35/286 (12.2%)‡</td>
<td>‡ 0.24</td>
</tr>
<tr>
<td>Non-TIMI III Flow §</td>
<td>54 (12.3%)</td>
<td>63 (14.3%)</td>
<td>0.37</td>
</tr>
<tr>
<td>TIMI I Flow</td>
<td>15 (3.4%)</td>
<td>2 (0.5%)</td>
<td>-</td>
</tr>
<tr>
<td>TIMI II Flow</td>
<td>3 (0.7%)</td>
<td>1 (0.2%)</td>
<td>-</td>
</tr>
<tr>
<td>TIMI III Flow</td>
<td>386 (87.7%)</td>
<td>377 (85.7%)</td>
<td>-</td>
</tr>
<tr>
<td>Angiographic String Sign</td>
<td>31 (7.1%)</td>
<td>4 (0.9%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Catheter Tip Spasm</td>
<td>50 (11.3%)</td>
<td>11 (2.5%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Non-Occlusive Angiographic Graft Stenoses:

<table>
<thead>
<tr>
<th>Proximal Anastomosis</th>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>None</td>
<td>275 (78.6%)</td>
<td>311 (88.9%)</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>1 - 30%</td>
<td>56 (16.0%)</td>
<td>32 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>31 - 70%</td>
<td>12 (3.4%)</td>
<td>5 (1.4%)</td>
<td></td>
</tr>
<tr>
<td>71 - 99%</td>
<td>7 (2.0%)</td>
<td>2 (0.6%)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Graft Body</th>
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</thead>
<tbody>
<tr>
<td>None</td>
<td>330 (94.3%)</td>
<td>307 (87.7%)</td>
<td>0.003 §</td>
</tr>
<tr>
<td>1 - 30%</td>
<td>14 (4.0%)</td>
<td>29 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>31 - 70%</td>
<td>4 (1.1%)</td>
<td>11 (3.1%)</td>
<td></td>
</tr>
<tr>
<td>71 - 99%</td>
<td>2 (0.6%)</td>
<td>3 (0.9%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distal Anastomosis</th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>301 (86.0%)</td>
<td>288 (82.3%)</td>
<td>0.15 §</td>
</tr>
<tr>
<td>1 - 30%</td>
<td>34 (9.7%)</td>
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<td>31 - 70%</td>
<td>8 (2.3%)</td>
<td>14 (4.0%)</td>
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</tr>
<tr>
<td>71 - 99%</td>
<td>7 (2.0%)</td>
<td>9 (2.6%)</td>
<td></td>
</tr>
</tbody>
</table>

* Includes TIMI 0, I, and II flow
† p = 0.03 for comparison of radial artery grafts with > 90% native vessel stenosis and radial artery grafts with < 90% native vessel stenosis
‡ p = 0.24 for comparison of saphenous vein grafts with > 90% native vessel stenosis and saphenous vein grafts with < 90% native vessel stenosis
§ p-value of McNemar test for no stenosis versus any stenosis comparing radial arteries and saphenous veins (paired) at the specified site in patients with no occluded grafts (n=350)
Table 6.4. Clinical Results for Patients with Triple-Vessel Coronary Disease receiving Radial Artery Graft to Right Coronary Artery or Circumflex Territory (n=561)

<table>
<thead>
<tr>
<th></th>
<th>30 Days</th>
<th>30 Days – 1 Year</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Death</td>
<td>4 (0.7%)</td>
<td>4 (0.7%)</td>
<td>8 (1.4%)</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>3 (0.5%)</td>
<td>2 (0.4%)</td>
<td>5 (0.9%)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>55 (9.8%)</td>
<td>1 (0.2%)</td>
<td>56 (10.0%)</td>
</tr>
<tr>
<td>Repeat Coronary Surgery</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Coronary Angioplasty</td>
<td>0 (0%)</td>
<td>4 (0.7%)</td>
<td>4 (0.7%)</td>
</tr>
<tr>
<td>Composite Endpoint *</td>
<td>58 (10.3%)</td>
<td>6 (1.1%)</td>
<td>65 (11.6%)</td>
</tr>
</tbody>
</table>

* Composite Endpoint = Cardiac death, non-fatal MI, or any repeat revascularization
Figure 6.1. Trial Summary
CHAPTER 7.

Impact of Patient and Target Vessel Characteristics on Arterial and Venous Bypass Graft Patency: Insight from a Randomized Trial

7.1 Abstract

**Background:** The purpose of this investigation is to determine optimal patient and target vessel characteristics to maximize arterial and venous graft patency using data from a large clinical trial.

**Methods and Results:** Angiographic data on 440 radial artery and 440 saphenous vein grafts were analysed using methodology to account for within-patient clustering. Multivariable models incorporating patient demographic, operative, anatomic, and post-discharge medical management were constructed to determine predictors of graft occlusion.

Radial artery use was strongly protective against graft occlusion at one-year after adjusting for all covariates, with a larger protective effect seen in women (p = 0.05 for a subgroup-by-treatment interaction). Among all grafts, diabetes and small target vessel diameter were associated with an increased risk of graft occlusion and grafting to a target vessel with more severe proximal stenosis was associated with a decreased risk of graft occlusion. With regard to gender, radial artery graft occlusion at one year occurred in similar proportions of men(8.6%) and women(5.3%, p=0.6), whereas, for saphenous vein grafts, the comparable occlusion rates were 12.0% and 23.3% respectively, p=0.02. A history of peripheral vascular disease was associated with an
elevated risk of radial artery occlusion but was not associated with early vein graft occlusion (p=0.02 for a subgroup-by-treatment interaction).

Conclusions: Patients benefit from radial artery coronary artery bypass conduits as opposed to saphenous vein conduits and this effect is especially strong in women. Small target vessel size adversely affected graft patency and grafting to a target vessel with more severe proximal stenosis improved graft patency.
IMPACT OF PATIENT AND TARGET VESSEL CHARACTERISTICS ON ARTERIAL AND VENOUS BYPASS GRAFT PATENCY: INSIGHT FROM A RANDOMIZED TRIAL

7.2 Background

We initiated the Multi-Centre Radial Artery Patency Study, a randomized clinical trial, to determine the relative patency of radial arteries to saphenous vein grafts. The primary results revealed that fewer radial artery grafts were totally occluded at one year compared to saphenous veins. The purpose of this investigation was to determine the impact of patient and target vessel characteristics on coronary bypass graft patency in order to develop recommendations for optimal conduit selection in multivessel bypass grafting.

7.3 Methods

Study Population: Details of the study protocol have been previously published. Patients aged less than 80 years undergoing non-emergent primary isolated coronary bypass surgery with graftable triple vessel disease and an estimated left ventricular ejection fraction greater than 35% were eligible for the study. The LITA was used to bypass the anterior circulation. Preoperative angiograms were assessed visually by the operating surgeon prior to randomization. The target coronary vessels for the study grafts were the left circumflex and the right coronary arteries, which, by protocol, had proximal lesions with at least 70% diameter narrowing, were greater than or equal to 1.5 mm in diameter and were deemed to be acceptable quality according to visual
assessment. The percent stenosis of proximal target vessel stenosis was coded in a continuous manner, size of target vessel and size of distal myocardial bed filled by the target vessel were coded in an ordinal fashion as small, medium, or large. Patients with a dominant circumflex coronary artery were eligible if they had sequential high grade lesions in the circumflex and suitable obtuse marginal and posterior descending branches. Patients were assessed preoperatively with a modified Allen’s Test to ensure adequate collateral circulation in the hand.

Randomization and Surgical Technique: All surgeries were performed using cardiopulmonary bypass and cardioplegic arrest. Patients were randomly assigned to one of two graft strategies: 1) The radial artery was used to graft the circumflex territory and a saphenous vein graft was used for the right coronary system; or, 2) the radial artery was directed to the right coronary territory and a saphenous vein graft was used for the circumflex system. The free radial artery pedicle was dilated in situ by a slow intraluminal injection of 4-5 ml of a dilute solution of verapamil and papaverine (5 mg verapamil and 65 mg of papaverine buffered in 16 ml of lactated Ringer’s solution). Two saphenous vein grafts and two radial artery grafts were used as sequential grafts. Two saphenous vein grafts and two radial artery grafts were used as Y-grafts.

Postoperative Medical Management: Patients were given aspirin 325 mg daily starting within six hours post-operatively and continued indefinitely. By protocol, patients received intravenous nitroglycerin 1-10 µg/kg/minute during the first 24 hours.
postoperatively in the intensive care unit. Vasoconstrictor agents were used only in
settings of significant peripheral vasodilatation by protocol. Oral nifedipine was
initiated on the first postoperative day and continued for six months post-operatively
for prophylaxis against radial artery spasm.

Follow-up Angiography: Patients were scheduled to undergo follow-up angiography 8
to 12 months following surgery. Nitroglycerin was injected into each graft prior to
filming. Postoperative angiograms were adjudicated in an independent, blinded fashion
by two cardiologists with a third review in the case of disagreement. Patency of only
the two randomized grafts (study radial artery and study saphenous vein) was
adjudicated. Grafts were determined to be occluded if no contrast dye injected into the
graft opacified the distal coronary artery (i.e. TIMI 0).

Statistical Methods: The primary endpoint of graft occlusion was calculated using the
McNemar Test for paired proportional data. Bivariate comparisons were performed
with chi squared test for dichotomous data and the continuous variables were compared
using Student’s T-test where appropriate. Multivariate predictors of radial artery and
saphenous vein occlusion were determined. Since the trial design was clustered, i.e. the
patient received both the study radial and control vein graft randomized to two different
territories, the occlusion rates of these two grafts were not independent of each
other.(128)
In these secondary analyses, within-patient clustering of graft occlusions was accounted for by using generalised estimating equations (GEE), a robust multivariable model.

Model predictors were specified apriori based on presumption that these were clinically relevant. These included: graft type (radial artery or saphenous vein), age in years (continuous), myocardial infarction with 30 days before operation (yes or no), gender (male or female), preoperative smoking status (yes = any history of smoking or no), preoperative diagnosis of diabetes (yes = any known diagnosis of diabetes before operation or no), preoperative history of hypertension (yes or no), preoperative history of hyperlipidemia (yes or no), preoperative history of any peripheral or cerebral vascular disease including stroke, transient ischemic attack, carotid endarterectomy, claudication, peripheral arterial angioplasty, bypass or endarterectomy surgery, or aneurysm repair (yes or no), left ventricular dysfunction with estimated global left ventricular ejection fraction (LVEF) of <35% (yes or no), proximal stenosis of target native coronary vessel graded by percent stenosis (continuous), size of target native coronary vessel graded on a visual scale in which vessel size was rated small, medium, or large (baseline) by the operating surgeon prior to operation based on visual assessment of the angiogram (categorical), number of bypass grafts (continuous), graft to the right coronary artery (yes or no), use of perioperative vasopressors (yes or no), aspirin prescribed at discharge (yes or no), calcium channel blocker therapy prescribed at discharge (yes or no), lipid lowering agent prescribed at discharge (yes or no). Our dataset also contained a qualitative assessment of the size of the distal myocardial bed.
size of the target vessel. As there was high correlation between the distal myocardial bed size of the target vessel and size of distal vessel (Pearson R = 0.8, p<0.0001), distal myocardial bed size was not included in any models.

Using the GEE model, overall predictors of graft occlusion in the study patients were determined. Tests of all 2-way statistical interactions between individual risk factors and graft type on graft occlusion revealed a significant differential effect of two risk factors on radial artery and saphenous vein graft occlusion (p<0.05 for interaction terms). These significant interaction terms were included in the final model.

Since differential effects of risk factors on arterial and venous grafts are biologically plausible, we created two regression models to determine risk factors for saphenous vein graft occlusion and radial artery occlusion individually (i.e. logistic regression). For these models, there is no within-patient clustering since each patient contributed data on one graft to each model. As there were relatively few clinical events (i.e. occluded grafts), we validated the logistic models using computer-intensive methods. Specifically, bootstrap estimates of odds ratios and 95% confidence intervals for each predictor were calculated from median values of 10,000 iterations of each logistic regression model.

Predictive models for graft patency (i.e. 1 minus the proportion of occluded grafts) were developed to compare the predicted graft patency for specific subgroups stratified by graft-type.
Statement of Responsibility: The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

7.4 Results

Patient Characteristics

Of 561 randomized patients, 440 eligible patients underwent coronary angiography at 12 months. As previously reported, there were no demographic differences between patients who were randomized and those who underwent study angiography.(5) Complete graft occlusion occurred in 13.6% (95% confidence interval 12.0% to 15.2%) of saphenous-vein grafts and 8.2% (95% confidence interval 6.9% to 9.5%) of radial-artery grafts (60 of 440 vs. 36 of 440, P=0.009 by McNemar’s test). The within-patient correlation for occlusion between graft types was 2.5% (95% CI -7% to 12%).

Medical therapy at discharge included: aspirin in 92.3%, other antithrombotic medications in 8.7%, lipid-lowering drugs in 66.7%, beta-blockers in 70.6%, and calcium channel blockers in 95.2% of patients.

Predictors of Graft Patency

Univariate analyses revealed significant differences in demographic profile between patients with occluded grafts and those with patent grafts.(see Table 7.1.) Saphenous vein grafts occlusion was more likely occur in female patients, diabetic patients, target vessels that were deemed small by visual assessment preoperatively, and in patients who were not discharged on daily aspirin. Radial artery graft occlusion was more
likely to occur in patients with peripheral vascular disease and among patients with target vessel proximal stenosis less than 90%. Hypertension and hyperlipidemia also tended to be more common among patients with occluded radial artery grafts.

Based on a multivariate model for all grafts, significant overall predictors of graft occlusion included: diabetes and small target coronary artery vessel. (see Table 7.2.). Grafting to a target vessel with more severe proximal stenosis was associated with a decreased risk of graft occlusion. Graft type was also a significant predictor, where radial arteries were significantly less likely to be occluded than saphenous veins (relative risk = 0.59, 95% confidence interval 0.37 to 0.92 versus saphenous veins). Tests of statistical interactions between individual patient risk factors of interest and graft occlusion revealed a significant differential effect of female gender (p=0.05 for interaction term) and history of peripheral vascular disease(p=0.02 for interaction term) on radial artery and saphenous vein graft patency. Interactions terms between graft type and severity of proximal target vessel stenosis(p=0.16 for interaction term) and size of distal target vessel were not statistically significant (p=0.28 for interaction term with small target vessel, p=0.56 for interaction term with medium target vessel).

Two distinct logistic regression models were also created to identify risk factors for radial artery and saphenous vein occlusion separately (See Tables 7.3. and 7.4. respectively). Preoperative history of peripheral vascular disease(OR 5.0, 95% CI 1.9 to 13.3) was a significant predictor of radial artery occlusion. Grafting to a target coronary artery with more severe proximal stenosis was protective (OR 0.95, 95% CI
0.93 to 0.99, for each 1% increase in percent proximal stenosis). Significant risk factors for vein graft occlusion included female gender (OR 2.3, 95% CI 1.1 to 5.0) and grafting to a smaller target coronary artery (OR 3.0, 95% CI 1.3 to 6.6, for comparison of grafting to a small target vessel versus a reference large target vessel). The effect of proximal stenosis appeared to be more prominent among radial artery grafts (OR=0.95 vs. 1.0 for veins) and that importance of small vessel size appeared more prominent in the vein grafts (OR=2.9 vs. 1.7 for arteries). In order to assess model fit, 10 000 iterations of each regression model were run in a bootstrap modelling procedure to determine median odds ratios and confidence intervals. Significant predictors of radial artery occlusion (peripheral vascular disease: OR 6.4, 95% CI 1.8 to 26.4 and less severe target vessel stenosis: OR 1.8, 95% CI 1.1 to 2.9) and saphenous vein graft occlusion (female gender: OR 2.4, 95% CI 1.0 to 5.7, and smaller target vessel size: OR 1.7, 95% CI 1.1 to 2.7) were similar to the original models.

**Impact of Target Vessel Characteristics**

Using parameter estimates from the logistic regression models, predictions of the expected graft patency of radial artery and saphenous veins, stratified by gender, were generated according to severity of proximal target vessel stenosis (Figure 7.1.) and size of target vessel (Figure 7.2.).

Grafting to target vessels with less than 90% proximal stenosis occurred in 154/440 (35.0%) saphenous vein grafts and 169/440 (38.4%) radial arteries (p=0.3). Target vessels with less than 90% stenosis were more common in grafts placed to the left circumflex coronary circulation 188/440 (42.7%) than those placed to the right.
coronary territory 135/440 (30.7%), p = 0.002. Among 169 radial arteries grafted to target vessels with less than 90% proximal stenosis, 156 (92%) were grafted to target vessels of medium or large calibre.

Small target vessel size was observed in 64/440 (14.5%) saphenous vein grafts and 49/440 (11.1%) of radial artery grafts. Among vein grafts, 17.5% of women and 14.1% of men had target coronary arteries rated as small (p=0.5). Among radial artery grafts, 8.7% of women and 11.5% of men had small coronary arteries (p=0.4). There was an imbalance in the proportions of vein grafts (17.5%) versus radial artery grafts (8.7%, p=0.2) anastomosed to small targets in women. There was no difference in proportion of small target vessels between the right and circumflex coronary systems. Among 64 saphenous veins grafted to small distal targets, 45 (70.3%) were grafted to target vessels with >90% proximal stenosis. A comparison of predicted radial artery and saphenous vein graft patency for varying rates of target vessel size and proximal stenosis revealed that radial artery grafting was superior regardless of target vessel size where the target vessel had at least 80-85% proximal stenosis. (see Figure 7.3.) Predicted vein graft patency was slightly higher than predicted radial artery graft patency when the proximal target coronary stenosis was 70% and the target vessel was large diameter.

**Differential Impact of Patient Characteristics**

Relative risks for each graft type stratified by gender and peripheral vascular disease were calculated using the GEE model and are presented in Figure 7.4. The risk
estimates for radial artery and saphenous vein graft occlusion in females with peripheral vascular disease had wide confidence intervals due to the limited number of subjects in these subgroups. Predicted graft patency from the overall regression model found that predicted graft patency for radial arteries in patients with peripheral vascular disease was 76.1% versus 95.2% for radial arteries in patients without peripheral vascular disease. For saphenous veins, predicted graft patency in patients with peripheral vascular disease was 83.4% versus 87.2% for saphenous veins in patients without peripheral vascular disease. With regard to gender, radial artery graft occlusion at one year occurred in similar proportions of men (8.6%) and women (5.3%, p=0.6), whereas, for saphenous vein grafts, the comparable occlusion rates were 12.0% and 23.3% respectively, p=0.02. Predicted radial artery patency was 94.0% in men and 97.0% in women. Predicted vein graft patency was 89.0% in men and 73.3% in women. The differential impact of gender on vein and radial graft patency is summarized by Figures 7.1 and 7.2.

7.5 Discussion

This clinical trial was designed to compare the patency of the radial artery and the saphenous vein as a coronary bypass graft at one year. To date, this is the largest prospective, randomized study with angiographic follow-up comparing patency of any arterial conduit to a saphenous vein when bypassing non-left anterior descending artery targets. The overall patency was superior for the radial artery and we have now identified risk factors which may guide selection of patients and target vessels for both saphenous vein and radial artery grafts to improve patency in patients undergoing coronary bypass with a LITA graft to the anterior circulation.
Overall predictors of bypass graft occlusion to non-LAD targets included use of a radial artery graft (protective), grafting to a target vessel with more severe proximal stenosis (protective), size of distal target vessel (small size is detrimental), gender (vein graft patency was poorer in women), diabetes (detrimental), and a history of peripheral vascular disease (detrimental in radial artery grafts). Previous studies have shown that patient and target vessel risk factors of arterial and vein graft patency may be different due to the inherent differences in the vascular biology of these conduits. We explored the relative effect of several risk factors stratified by graft type and determined that two variables, female gender and history of peripheral vascular disease, had differential effects on graft patency depending on the conduit used (saphenous vein or radial artery). Target vessel characteristics including severity of proximal stenosis and target vessel size affected saphenous vein graft and radial artery patency. Indeed, the directional effect of smaller target vessel diameter was to decrease graft patency in both radial artery and vein grafts. The magnitude of this effect appeared to be more prominent for vein grafts. Similarly, less severe proximal stenosis was associated with diminished patency in both types of grafts with a more prominent effect seen in radial arteries.

**Role of Target Vessel Characteristics**

**Target Vessel Location:** Since the unit of randomization was the target vessel location within the patient, the study was uniquely designed to determine the role of target vessel location on arterial and vein graft patency. In our multivariate model, there was
no difference in patency of either graft type when used to bypass the right coronary or left circumflex systems. Several angiographic trials have previously documented that while vein graft patency is superior when revascularizing the LAD, there is no difference in vein graft patency between right coronary and left circumflex targets. Target location appears to have a consistent association with right internal thoracic artery (RITA) graft patency, with poorer patency seen in RITA grafts to the right coronary system. This study and others suggest that such a relationship does not exist with radial arteries, even when controlling for severity of target vessel stenosis. Early RITA graft attrition in the right coronary territory may be due to inadequate length using an in-situ RITA graft to the posterior interventricular branch, a problem less often encountered when using either a free RITA graft or a radial artery. Alternatively, when the RITA is used to bypass more proximally on the right coronary artery, progression of downstream disease may eventually compromise graft outflow and lead to early occlusion.

**Target Vessel Size:** Several factors may lead to diminished patency in conduits grafted to smaller target vessels. Size mismatch, particularly when larger (3.5-4 mm) saphenous veins, are grafted to small targets may predispose to impaired, non-laminar flow patterns resulting in stimulus for endothelial dysfunction and early intimal hyperplasia or graft occlusion. Small distal targets may be more technically difficult to graft and may have significant disease at or adjacent to the anastomotic site itself. Larger calibre target vessels may also have better distal run-off. Distal bed size by
subjective visual assessment was recorded at the time of study enrolment and was highly correlated with the size of distal target vessel.

**Severity of Proximal Stenosis:** We also found a significant relationship between graft patency and severity of proximal target vessel stenosis. Despite highly selective entry criteria which mandated the target vessels have greater than 70% stenosis, we observed a significant gradient in radial graft patency with decreasing severity of the proximal target lesion. Although we did not directly measure intraoperative graft flows in this study, we and others have hypothesized that the mechanism of failure in these grafts is likely flow competition from the native coronary vessel.\(^{(188;203;234)}\) We have previously reported that among patent radial arteries, diffuse narrowing, known as angiographic string sign, is also a consequence of competitive flow.\(^{(328)}\) We speculate that in the setting of competitive flow, progressive auto-regulated adaptive narrowing of the radial conduit may eventually lead to graft occlusion. Although the signalling mechanism by which flow competition provides a stimulus for graft dysfunction has not been well characterized, low flow and resultant low shear stress in the radial conduit may impair endothelial function.\(^{(329)}\) Among various arterial conduits, the radial artery is known to have a greater contractile response to a variety of stimuli, presumably due to greater myocyte density in the media layer. Flow competition may also occur in the setting of high volume flow from collateral vessels even when the target vessel has a high grade stenosis. Such relationships were not explored in this analysis.
Patient Characteristics

**Diabetes:** Diabetes was associated with an elevated risk of graft attrition in this study. These findings are congruent with previous longitudinal angiographic studies by Sabik and colleagues examining over 10,000 venous and internal thoracic artery arterial bypass grafts.\(^{(187)}\) The impact of diabetes on a wide variety of metabolic processes leads to more rapid progression of atherosclerosis. The effect of diabetes on graft patency is, however, not consistent among angiographic studies. Follow-up studies by Shah and colleagues and the Bypass Angioplasty Revascularization Investigation (BARI) did not find diabetes to be a significant risk factor for saphenous graft attrition in follow-up.\(^{(330)}\) We had no information on glycemic control preoperatively or postoperatively in these patients.

**Gender:** The impact of gender on patency outcomes of coronary surgery has been difficult to assess due to the limited number of female patients recruited in clinical trials, including the current study. Seminal prospective post-operative patency studies from the Veteran’s Affairs System as well as Fitzgibbon included only male subjects.\(^{(38;331)}\) Seven percent of the patients enrolled in the Post-CABG Study\(^{(126)}\) and 13\% of patients enrolled in the CABADAS Study\(^{(235)}\) were female. Due to the limited sample size of female patients in these and other angiography studies, meaningful sub-group analyses of the role of gender in vein graft patency are often underpowered. In the Post-CABG investigation, although female gender was associated with diminished graft occlusion, no information regarding the age of female patients at the time of operation was provided. In the CABADAS trial, the mean age of female patients was 61 years versus 58 years for men and there was a modest but not
significant increase in graft occlusion in women (OR 1.6, p=0.1). Our study also enrolled 13% female patients with a mean age of 64.3 years versus 60.3 years in men and only 5% of female patients were less than 50 years old. In this study, women were more likely to experience early vein graft attrition and this gender effect was not present in radial arteries. Additionally, we have demonstrated that the effect of female gender on vein graft patency exists independent of target vessel size and that gender did not influence target vessel size in the patients selected for this clinical trial. This observation has previously been described in a series of consecutive patients prospectively followed.\(^{(332)}\) Changes in inflammatory cytokine milieu in post-menopausal women may lead to the observed acceleration in vein graft disease. Multiple arterial grafting does appear, in this early patency study, to be a vastly superior approach in post-menopausal women.

**Peripheral Vascular Disease:** Our study protocol excluded patients with a history of severe peripheral vascular disease due to concerns regarding the safety of follow-up angiography. Previous studies have shown that a history of peripheral vascular disease is associated with an increased risk of radial artery atherosclerosis at the time of harvest.\(^{(258)}\) Using intravascular ultrasound, the overall proportion of in-situ radial arteries before harvest with at least one discrete >50% narrowing is estimated to be up to 8.6% and a further 8.6% have non-hemodynamically significant calcification.\(^{(333)}\) In this trial, patients with a history of peripheral vascular disease were significantly more likely to experience early graft failure. Many radial artery grafts in these patients may have had subclinical atherosclerosis at the time harvest. We recommend against the use of the radial artery in patients with peripheral vascular disease as the likelihood
of occlusion is greater than that of saphenous vein occlusion. Preoperative ultrasound examination of the radial arteries in patients with peripheral vascular disease could potentially be used to identify subclinical atherosclerosis. There was insufficient data regarding the concurrent effects of peripheral vascular disease and female gender on graft patency in this study to determine with confidence the ideal conduit in women with peripheral vascular disease.

*Optimization of Revascularization Strategy:*

Based on predictions from our multivariate models, optimal selection of the target vessel can improve graft patency in saphenous vein and radial artery grafts. Radial arteries grafted to severely stenotic targets (>90%) are expected to have a one year patency approaching that of an internal mammary artery grafted to the anterior circulation of the heart. In this trial, surgeons were not permitted to deviate from the randomized target vessel and consequently, variation in severity of proximal stenosis and size of distal targets was observed. In most instances where small target vessel size appeared to negatively influence vein graft patency, that target vessel had a higher grade proximal stenosis and an arterial conduit could be expected to have excellent patency. Similarly, in most instances where competitive flow compromised radial artery patency, the target vessel size was medium or large and a vein graft could be expected to have adequate patency, at least in men.
**Study Limitations**

This study was a secondary analysis of a multicenter clinical trial. We did not have baseline or follow-up laboratory documentation of lipid levels, glycemic control, or inflammatory markers. Although the present study is one of the largest coronary surgery clinical trials with angiographic endpoints, sample size was somewhat limited in certain subgroups. The severity of the target stenosis and size of the target vessel were derived from single observer visual assessment at the time of patient enrolment and not quantitative angiography. Previous studies have shown that visual assessment tends to overestimate the severity of stenosis in comparison to quantitative angiography.\(^{(322)}\) We did not have accurate information about the location of vein graft harvest site (thigh versus calf) or intraoperative luminal diameter of the bypass conduit.

**Conclusions**

Target vessel characteristics significantly influence both radial artery and saphenous vein graft patency. Optimal patency rates are experienced when radial arteries are grafted to target vessels with severe proximal stenosis and when vein grafts are grafted to larger target vessels. Radial artery use in patients with a known preoperative history of peripheral vascular disease should be avoided and there is a preferential advantage to multiple arterial grafting in women.
### Table 7.1. Baseline Characteristics of Patients According to Graft Type and Patency Status at One Year

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient Vein Grafts (n=380)</th>
<th>Occluded Vein Grafts (n=60)</th>
<th>P-Value*</th>
<th>Patient Radial Grafts (n=404)</th>
<th>Occluded Radial Grafts (n=36)</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60.6±8.4</td>
<td>61.8±8.0</td>
<td>0.32</td>
<td>60.7±8.5</td>
<td>61.3±7.5</td>
<td>0.68</td>
</tr>
<tr>
<td>Age &gt;70</td>
<td>60 (15.8)</td>
<td>8 (13.3)</td>
<td>0.62</td>
<td>63 (15.6)</td>
<td>5 (13.9)</td>
<td>0.89</td>
</tr>
<tr>
<td>Preoperative MI</td>
<td>178 (46.8)</td>
<td>26 (43.4)</td>
<td>0.61</td>
<td>185 (45.8)</td>
<td>19 (52.8)</td>
<td>0.49</td>
</tr>
<tr>
<td>Male Gender</td>
<td>337 (88.7)</td>
<td>46 (76.7)</td>
<td>0.02</td>
<td>350 (86.6)</td>
<td>33 (91.7)</td>
<td>0.60</td>
</tr>
<tr>
<td>Female Gender</td>
<td>43 (11.3)</td>
<td>14 (23.3)</td>
<td></td>
<td>54 (13.4)</td>
<td>3 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>276 (72.6)</td>
<td>41 (68.3)</td>
<td>0.49</td>
<td>288 (71.3)</td>
<td>29 (80.6)</td>
<td>0.23</td>
</tr>
<tr>
<td>Diabetes</td>
<td>93 (24.5)</td>
<td>22 (36.7)</td>
<td>0.05</td>
<td>104 (25.7)</td>
<td>11 (30.6)</td>
<td>0.53</td>
</tr>
<tr>
<td>Hypertension</td>
<td>171 (45.0)</td>
<td>32 (53.3)</td>
<td>0.23</td>
<td>181 (44.8)</td>
<td>22 (61.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>Elevated Lipids</td>
<td>257 (67.6)</td>
<td>46 (76.7)</td>
<td>0.16</td>
<td>273 (67.6)</td>
<td>30 (83.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>LV Function **</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>185 (48.7)</td>
<td>28 (46.7)</td>
<td></td>
<td>197 (48.7)</td>
<td>16 (44.4)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>188 (49.5)</td>
<td>32 (53.3)</td>
<td></td>
<td>201 (49.7)</td>
<td>19 (52.7)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6 (1.5)</td>
<td>0 (0)</td>
<td>0.05</td>
<td>5 (1.2)</td>
<td>1 (2.8)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1 (0.3)</td>
<td>0 (0)</td>
<td>0.72</td>
<td>1 (0.25)</td>
<td>0 (0)</td>
<td>0.84</td>
</tr>
<tr>
<td>Proximal Stenosis of Target Vessel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-79.9%</td>
<td>79 (20.8)</td>
<td>10 (16.7)</td>
<td></td>
<td>76 (18.8)</td>
<td>13 (36.1)</td>
<td></td>
</tr>
<tr>
<td>80-89.9%</td>
<td>50 (13.2)</td>
<td>15 (25.0)</td>
<td></td>
<td>73 (18.1)</td>
<td>7 (19.4)</td>
<td></td>
</tr>
<tr>
<td>90-99.9%</td>
<td>132 (34.7)</td>
<td>15 (25.0)</td>
<td></td>
<td>126 (31.2)</td>
<td>9 (25.0)</td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td>119 (31.3)</td>
<td>20 (33.3)</td>
<td>0.24</td>
<td>129 (31.9)</td>
<td>7 (19.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Target Vessel Size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>48 (12.6)</td>
<td>16 (26.7)</td>
<td></td>
<td>43 (10.6)</td>
<td>6 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>173 (45.5)</td>
<td>27 (45.0)</td>
<td>0.009</td>
<td>189 (46.8)</td>
<td>15 (41.7)</td>
<td>0.53</td>
</tr>
<tr>
<td>Large</td>
<td>159 (41.8)</td>
<td>17 (28.5)</td>
<td>0.009</td>
<td>172 (42.6)</td>
<td>15 (41.7)</td>
<td>0.53</td>
</tr>
<tr>
<td>Number of Grafts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>142 (37.4)</td>
<td>16 (26.7)</td>
<td></td>
<td>144 (35.6)</td>
<td>14 (38.9)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>190 (50.5)</td>
<td>38 (63.3)</td>
<td></td>
<td>212 (52.5)</td>
<td>16 (44.4)</td>
<td></td>
</tr>
<tr>
<td>5 or more</td>
<td>48 (12.6)</td>
<td>6 (10.0)</td>
<td>0.16</td>
<td>48 (11.9)</td>
<td>6 (16.7)</td>
<td>0.57</td>
</tr>
<tr>
<td>Graft Location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCA Territory</td>
<td>189 (49.8)</td>
<td>30 (50)</td>
<td></td>
<td>202 (50)</td>
<td>17 (47.2)</td>
<td>0.89</td>
</tr>
<tr>
<td>LCX Territory</td>
<td>191 (50.2)</td>
<td>30 (50)</td>
<td>1.0</td>
<td>202 (50)</td>
<td>19 (52.8)</td>
<td>0.30</td>
</tr>
<tr>
<td>Perioperative Use of Vasopressors</td>
<td>15 (4.0)</td>
<td>1 (1.7)</td>
<td>0.38</td>
<td>13 (3.2)</td>
<td>3 (8.3)</td>
<td>0.14</td>
</tr>
<tr>
<td>ASA at Discharge</td>
<td>357 (94.0)</td>
<td>52 (86.7)</td>
<td>0.05</td>
<td>377 (93.3)</td>
<td>32 (88.9)</td>
<td>0.31</td>
</tr>
<tr>
<td>CCB at Discharge</td>
<td>361 (95.0)</td>
<td>58 (96.7)</td>
<td>0.57</td>
<td>386 (95.5)</td>
<td>33 (91.7)</td>
<td>0.30</td>
</tr>
<tr>
<td>LLA at Discharge</td>
<td>265 (69.7)</td>
<td>44 (73.3)</td>
<td>0.64</td>
<td>279 (69.0)</td>
<td>30 (83.3)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

ASA = aspirin; CCB = calcium-channel blocker; LLA = lipid lowering agent
PVD = peripheral vascular disease; LV Function = Left ventricular function; RCA = Right Coronary Artery; LCX = Left Circumflex Coronary Artery

* For comparison of males to females for each graft type
** LV Function was graded according to the following scale: Grade of 1= estimated global left ventricular ejection fraction (LVEF) of 50 or more; Grade of 2= LVEF of 35 to 49; Grade of 3= LVEF of 20 to 34; Grade of 4 = LVEF of less than 20.
† For comparison of proximal stenosis ≥90% versus proximal stenosis ≤90%; p=0.08 for overall trend
‡ For comparison of proximal stenosis ≥90% versus proximal stenosis ≤90%; p=0.07 for overall trend
¶ P-value testing null hypothesis that patent and occluded groups have the same mean or the same distribution across categories.
Table 7.2. Multivariate Predictors* of Saphenous Vein and Radial Artery Occlusion at One Year

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial Artery Graft</td>
<td>0.59</td>
<td>(0.37, 0.92)</td>
<td>0.02</td>
</tr>
<tr>
<td>Age (in Years)</td>
<td>1.01</td>
<td>(0.99, 1.04)</td>
<td>0.27</td>
</tr>
<tr>
<td>Preoperative MI</td>
<td>1.11</td>
<td>(0.78, 1.60)</td>
<td>0.58</td>
</tr>
<tr>
<td>Female Gender</td>
<td>1.78</td>
<td>(1.11, 2.84)</td>
<td>0.02</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.96</td>
<td>(0.65, 1.41)</td>
<td>0.82</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.45</td>
<td>(1.03, 2.05)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.33</td>
<td>(0.91, 1.92)</td>
<td>0.14</td>
</tr>
<tr>
<td>Elevated Lipids</td>
<td>1.56</td>
<td>(0.89, 2.71)</td>
<td>0.12</td>
</tr>
<tr>
<td>PVD History</td>
<td>1.05</td>
<td>(0.45, 2.42)</td>
<td>0.91</td>
</tr>
<tr>
<td>LV Ejection Fraction** &lt;35%</td>
<td>0.75</td>
<td>(0.1, 5.4)</td>
<td>0.78</td>
</tr>
<tr>
<td>Target Proximal Stenosis†</td>
<td>0.98</td>
<td>(0.97, 0.99)</td>
<td>0.02</td>
</tr>
<tr>
<td>Target Vessel Size‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>2.28</td>
<td>(1.47, 3.55)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Medium</td>
<td>1.22</td>
<td>(0.79, 1.87)</td>
<td>0.35</td>
</tr>
<tr>
<td>Large</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of Bypass Grafts §</td>
<td>1.22</td>
<td>(0.92, 1.64)</td>
<td>0.17</td>
</tr>
<tr>
<td>Right Coronary Graft</td>
<td>1.05</td>
<td>(0.73, 1.50)</td>
<td>0.80</td>
</tr>
<tr>
<td>Perioperative Vasopressors</td>
<td>1.11</td>
<td>(0.68, 1.81)</td>
<td>0.68</td>
</tr>
<tr>
<td>ASA at Discharge</td>
<td>0.73</td>
<td>(0.40, 1.31)</td>
<td>0.32</td>
</tr>
<tr>
<td>CCB at Discharge</td>
<td>1.23</td>
<td>(0.41, 3.72)</td>
<td>0.31</td>
</tr>
<tr>
<td>LLA at Discharge</td>
<td>1.10</td>
<td>(0.67, 1.78)</td>
<td>0.70</td>
</tr>
<tr>
<td>Graft Type by Gender Interaction</td>
<td></td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Graft Type by PVD History Interaction</td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
</tbody>
</table>

ASA = aspirin; CCB = calcium-channel blocker; LLA = lipid lowering agent; PVD = peripheral vascular disease; LV = Left ventricular; MI = myocardial infarction

* Multivariate predictors derived from generalized estimating equations model including data on all 440 saphenous vein grafts and 440 radial artery grafts (total N=880 grafts).
** Estimated global left ventricular ejection fraction
† Percent Stenosis of the most significant proximal lesion in native target coronary vessel (continuous variable)
‡ Graded on a subjective visual scale (small, medium or large) by the operating surgeon based on preoperative review of the angiogram
§ Number of bypass grafts (continuous variable)
Table 7.3. Multivariate Predictors of Radial Artery Graft Occlusion at One Year

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.1</td>
<td>(0.4,3.1)</td>
</tr>
<tr>
<td>Preoperative MI</td>
<td>1.3</td>
<td>(0.6,2.9)</td>
</tr>
<tr>
<td>Female Gender</td>
<td>0.4</td>
<td>(0.1,1.7)</td>
</tr>
<tr>
<td>Smoker</td>
<td>1.3</td>
<td>(0.5,3.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.1</td>
<td>(0.4,2.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.8</td>
<td>(0.8,3.9)</td>
</tr>
<tr>
<td>Elevated Lipids</td>
<td>1.6</td>
<td>(0.6,4.6)</td>
</tr>
<tr>
<td><strong>PVD History</strong></td>
<td><strong>5.0</strong></td>
<td><strong>(1.9,13.3)</strong></td>
</tr>
<tr>
<td>LV Function *</td>
<td>1.6</td>
<td>(0.8,3.3)</td>
</tr>
<tr>
<td><strong>Target Proximal Stenosis</strong>†</td>
<td><strong>0.95</strong></td>
<td><strong>(0.93,0.99)</strong></td>
</tr>
<tr>
<td>Target Vessel Size ‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>1.7</td>
<td>(0.8,3.7)</td>
</tr>
<tr>
<td>Medium</td>
<td>1.1</td>
<td>(0.6, 1.7)</td>
</tr>
<tr>
<td>Large</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA at Discharge</td>
<td>1.0</td>
<td>(0.3,3.5)</td>
</tr>
<tr>
<td>CCB at Discharge</td>
<td>0.4</td>
<td>(0.1,1.6)</td>
</tr>
<tr>
<td>LLA at Discharge</td>
<td>2.0</td>
<td>(0.7,5.7)</td>
</tr>
</tbody>
</table>

ASA = aspirin; CCB = calcium channel blockers; LLA = lipid lowering medications including statins and fibrates.

* LV Function was graded according to the following scale: Grade of 1= estimated global left ventricular ejection fraction (LVEF) of 50 or more; Grade of 2= LVEF of 35 to 49; Grade of 3= LVEF of 20 to 34; Grade of 4 = LVEF of less than 20. In this model, comparisons are made against a baseline LV Function of 1.
† Percent Stenosis of the most significant proximal lesion in native target coronary vessel (continuous variable)
‡ Graded on a subjective visual scale (small, medium or large) by the operating surgeon based on preoperative review of the angiogram
§ Number of bypass grafts (continuous variable)
Table 7.4. Multivariate Predictors of Saphenous Vein Graft Occlusion at One Year

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.9</td>
<td>(0.4, 1.9)</td>
</tr>
<tr>
<td>Preoperative MI</td>
<td>1.0</td>
<td>(0.5, 1.8)</td>
</tr>
<tr>
<td><strong>Female Gender</strong></td>
<td><strong>2.3</strong></td>
<td><strong>(1.1, 5.0)</strong></td>
</tr>
<tr>
<td>Smoker</td>
<td>0.8</td>
<td>(0.4, 1.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.6</td>
<td>(0.8, 2.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.2</td>
<td>(0.7, 2.0)</td>
</tr>
<tr>
<td>Elevated Lipids</td>
<td>1.4</td>
<td>(0.7, 2.9)</td>
</tr>
<tr>
<td>PVD History</td>
<td>1.2</td>
<td>(0.4, 3.7)</td>
</tr>
<tr>
<td>LV Function*</td>
<td>1.0</td>
<td>(0.6, 1.8)</td>
</tr>
<tr>
<td>Target Vessel Stenosis†</td>
<td>1.4</td>
<td>(0.8, 2.5)</td>
</tr>
<tr>
<td><strong>Target Vessel Size‡</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>3.0</td>
<td>(1.3, 6.6)</td>
</tr>
<tr>
<td>Medium</td>
<td>1.4</td>
<td>(0.8, 2.4)</td>
</tr>
<tr>
<td>Large Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA at Discharge</td>
<td>0.5</td>
<td>(0.2, 1.2)</td>
</tr>
<tr>
<td>CCB at Discharge</td>
<td>1.7</td>
<td>(0.3, 8.3)</td>
</tr>
<tr>
<td>LLA at Discharge</td>
<td>0.9</td>
<td>(0.5, 1.8)</td>
</tr>
</tbody>
</table>

ASA = aspirin; CCB = calcium channel blockers; LLA = lipid lowering medications including statins and fibrates.

* LV Function was graded according to the following scale: Grade of 1 = estimated global left ventricular ejection fraction (LVEF) of 50 or more; Grade of 2 = LVEF of 35 to 49; Grade of 3 = LVEF of 20 to 34; Grade of 4 = LVEF of less than 20. In this model, comparisons are made against a baseline LV Function of 1.
† Percent Stenosis of the most significant proximal lesion in native target coronary vessel (continuous variable)
‡ Graded on a subjective visual scale (small, medium or large) by the operating surgeon based on preoperative review of the angiogram
§ Number of bypass grafts (continuous variable)
Figure 7.1. Impact of Severity of Proximal Target Vessel Stenosis on Radial Artery and Saphenous Vein Graft Patency
**Figure 7.2.** Impact of Size of Distal Target Vessel on Radial Artery and Saphenous Vein Graft Patency
**Figure 7.3.** Impact of Severity of Proximal Target Stenosis and Size of Distal Target Vessel on Radial Artery and Saphenous Vein Graft Patency Stratified by Graft Type
**Figure 7.4.** Relative Risk for Graft Occlusion at One Year For Radial Artery and Saphenous Vein Grafts Stratified According to Gender and Presence or Absence of Peripheral Vascular Disease (PVD)

* p < 0.05
Chapter 8

General Discussion and Conclusions

8.1 General Discussion

From the early adventures of pioneers such as Alexis Carrel to improve blood flow to the heart to the systematic approach applied by Dudley Johnson, coronary surgery has evolved into a precise, reproducible and highly successful procedure performed throughout the world. Large scale clinical trials documented its superiority over medical therapy and although recent innovations in coronary stenting have led to a small decline in surgical volume, coronary bypass surgery remains the treatment of choice in patients with complex coronary disease and remains the only procedure which provides survival benefit in patients with stable angina. Despite its success, there is still a lack of consensus regarding fundamental aspects to the performance of coronary surgery. The role of off-pump surgery remains undefined. Image-guidance, now routine in many other surgical specialties, is not routinely used for quality assurance of the bypass graft. Multiple arterial grafting, although considered by many if not most surgeons to provide superior patency outcomes, is not common and the question of which conduit is the ideal second arterial graft remains unanswered.

In this thesis, strategies to improve the outcomes of coronary artery bypass surgery were investigated using a variety of prospective study methodologies. The overall aim was to determine techniques that could be applied in the operating room to improve graft patency. In the introductory chapter, we elaborated on the validity of graft patency as a predictor of long term clinical outcomes to provide the scientific basis for
using graft patency as a meaningful endpoint for our studies. Graft patency measurement, although a highly invasive method of endpoint assessment, allows for smaller sample sizes and shorter follow-up periods as graft failure, a valid surrogate marker for late myocardial infarction and mortality, occurs earlier and, initially, often silently.

We began our investigations with a comprehensive survey of physician utilization and attitudes regarding evolving coronary bypass techniques such as off-pump surgery, intraoperative graft patency assessment and arterial grafting. Concern regarding increased technical failures in off-pump surgery led to the emergence of various technologies for intraoperative graft assessment and we performed prospective investigations including early human trials and a clinical trial assessing the efficacy of indocyanine green angiography to detect technical errors in coronary bypass grafts and compare it to well established techniques. We also pooled data from our studies to demonstrate the effect of graft patency assessment on the clinical endpoint of perioperative myocardial injury. Multiple arterial grafting has been proposed to reduce early graft attrition seen in saphenous veins. We determined the relative patency of the radial artery conduit versus the saphenous vein using a large multicentre clinical trial and further delineated optimum graft selection based on patient and angiographic features using complex multivariable modeling.

Our survey of Canadian heart surgeons showed several interesting trends in the utilization of emerging therapies in coronary bypass surgery. The overall utilization of
off-pump surgery, intraoperative graft imaging and multiple arterial grafting were low among Canadian surgeons. Only 16% of coronary bypass cases performed in 2002 were performed off-pump, the majority of surgeons performed multiple arterial grafting in less than 25% of cases (and most frequently less than 5%) and less than 10% of surgeons used any method of graft patency assessment routinely, although its usage was higher in off-pump cases. The survey confirmed that innovative techniques and technologies have not gained significant utilization and provide the rationale for our studies aimed at operative strategies to improve graft patency.

8.2 Appraisal of Study Hypothesis 1

**Intraoperative graft assessment with indocyanine green angiography is feasible and provides high quality anatomic detail that is superior to currently used methodologies to identify graft problems.**

Early graft occlusion is generally ascribed to intraoperative technical failure and is responsible for poorer freedom from clinical events. Despite the tremendous number of coronary bypass procedures performed world-wide, no routine standard of care regarding graft assessment has been established. Transit-time flowmetry gained popularity in the 1990s as a method of counteracting elevated graft failure rates observed in off-pump surgery but has not gained significant implementation. We believe this may be, in part, be due to inherent difficulties in interpreting transit time flow data that is not intuitive to surgeons, who are more familiar with angiographic depictions. Our initial clinical use of indocyanine green angiography, a technology innovated and commercialized by a Canadian company, suggested that this form of graft assessment may provide highly accurate graft patency assessment in a fairly rapid
and user-friendly manner. Our investigations of the technology started with early dose-finding and timing studies to achieve optimal graft angiographic image sequences. In our initial series, we demonstrated that ICG angiography was able to rapidly produce high quality images that were similar to angiographic images achieved with conventional x-ray angiography. The technique had excellent inter-rater reliability for determining graft occlusion and need for graft revision. Over 4% of patients were found to have technical errors in graft that would have otherwise gone unrecognized. We also determined that saphenous vein grafts, which generally have the highest technical failure rates, were best visualized with this technology. Arterial grafts often required the additional maneuver of removing the overlying pedicle tissue to allow good visualization of the anastomosis.

This preliminary investigation of ICG angiography showed the technology had promise as a standard quality control measure in coronary bypass surgery. Our next investigation was designed to determine if ICG angiography was superior to transit-time flow measurement in its ability to detect graft errors. The study was designed using very early post-operative x-ray angiography or pathological assessment as the reference standard to determine sensitivity and specificity. To our knowledge, no previous studies had documented these measures of diagnostic accuracy for ICG angiography or even TTF, despite its widespread clinical use. Our study was designed to be highly efficient in terms of number of patients needing to undergo post-operative angiography and a so a within patient randomization scheme was used enabling the same graft to be studied using the three techniques (ICG angiography, TTF, and reference standard) in an unbiased fashion. We had apriori anticipated a significant
drop-out rate between the patients agreeing to participate preoperatively and those actually willing to undergo the post-operative day four angiogram, as this was a fairly invasive test that was not generally part of routine care. Our principal finding was that ICG angiography provided superior sensitivity to detect graft errors versus TTF.

Although the number of true-positives was too small in our study to do subgroup analyses, the greatest difference between the techniques appeared to be in the ability to detect errors in grafts that were not totally occluded but had greater than 50% stenosis. We also found that the actual point estimate of sensitivity (25%) for TTF was much lower than expected. Diameter stenoses generally must be greater than 70-75% to affect volumetric flow rate at rest. Hence, only very high grade stenoses can be identified with purely flow based methods of graft assessment. Anatomic methods of graft assessment such as ICG angiography appear to less affected by these limitations and may be more ideally suited for the purpose of intraoperative graft assessment.

Our study examining perioperative myocardial injury provided further corroboration of our presumption that identifying and correcting intraoperative graft failures may result in better clinical outcomes. We express some caution in the reporting of these findings due to the retrospective nature of this study, the heterogeneous study populations and the use of a less well validated endpoint of elevated troponins as a marker for future clinical events. Nonetheless, this preliminary study suggests that avoidance of intraoperative graft failure with imaging may have an effect on clinical outcomes of similar magnitude to well established, routine practices such as the early use of aspirin after surgery.
8.3 Appraisal of Study Hypothesis 2

Radial artery grafts will have superior patency than saphenous vein grafts.

Patient and target vessel characteristics have a significant effect on graft patency, and due to their intrinsically distinct biology, the factors for graft failure between graft types will be different.

Perhaps the greatest unanswered question in coronary surgery today is how to optimally select conduits for bypass other than the LITA. As discussed in our introductory chapter and verified in our survey of Canadian heart surgeons, the use of a second arterial conduit in coronary surgery is uncommon. We believe that the major barriers to implementation include difficulty of use (conduit length etc.) and concern regarding wound complications for the RITA and lack of prospective graft patency data for the radial artery. To address the role of the radial artery as a bypass conduit, we undertook a large multicentre randomized clinical trial with one year angiographic follow-up comparing radial artery and saphenous vein graft patency. In order maximize efficiency, we used a study design in which patients contributed both the active intervention (radial artery) and control (saphenous vein) so that the number of patients requiring follow-up angiography could be minimized as this was a fairly invasive test. Randomization of the target vessel also eliminated target vessel selection biases which influence virtually all angiographic studies.

We found that radial arteries had superior absolute patency versus saphenous veins. The enhanced patency of the radial artery was attenuated by the presence of competitive flow from the native target vessel when the proximal lesion was less
severe. In these cases, the radial artery underwent diffuse narrowing leading to an angiographic 'string sign'. Indeed, when we applied the more stringent measure of 'perfect' graft patency, we did not observe a difference between conduit types. This finding lessened our ability to strongly propose that the radial artery should be used preferentially in all bypass patients - a statement which would have had far-reaching clinical implications for the 500,000+ patients undergoing coronary bypass surgery annually.

Instead, we set out to further delineate in which specific circumstances the radial artery performed better. In doing so, we established an individualized approach to conduit selection in which specific patient and target vessel characteristics that led to improved outcomes with either conduit type were identified. The within-patient randomization feature of the study design, although efficient, led to larger challenges in multivariate subgroup analysis as assumptions regarding independence between grafts that are intrinsic to standard logistic regression models were violated since each patient provided two grafts. To overcome these difficulties, we created a generalized estimating equations model in which the patency of each graft functioned as an individual outcome but co-linearity was accounted for by using a linking term identifying grafts from the same patient.

The model identified anatomic factors of the target vessel that significantly affect graft patency including absolute size and presence of competitive flow. These findings are important as they suggest that a highly individualized approach to conduit selection incorporating target vessel and patient characteristics can maximize graft patency. Importantly, the data required to make these decisions is available from the
preoperative angiogram and patient history allowing preoperative creation of the grafting strategy.

Further studies have been initiated to clarify the role of intraoperative graft imaging in coronary surgery. The GRaft Imaging to Improve Patency (GRIIP) trial, funded by the Heart and Stroke Foundation of Ontario has been initiated to determine if a strategy of intraoperative patency assessment and graft revision can decrease the rate of graft occlusion or significant stenosis (>50%) at 6-12 weeks after coronary artery bypass grafting (CABG) versus traditional operative management without routine intraoperative patency assessment. Patency will be assessed with indocyanine green angiography as well as ultrasonic transit-time flow measurement. The study is a randomized controlled single-centre clinical trial and aims to recruit 270 patients in each group over a four year recruitment period. Endpoint assessment will include both traditional catheter based x-ray angiography, and as the technology develops, very high resolution CT angiography to determine graft patency. Other studies are also underway to define the outcomes of radial artery grafting including a large randomized clinical trial by the Veteran Affairs Administration (ClinicalTrials.gov Identifier: NCT00054847) Unlike our study, this study uses a more traditional between patient randomization scheme which will allow for clinical outcome determination in addition to graft patency. Also, a multicentre trial in the United Kingdom is underway to assess the role of bilateral internal thoracic artery grafting on late clinical outcomes. (WHO International Clinical Trials Registry: ISRCTN46552265)

Also, a five-year follow-up of the Radial Artery Patency Study is well underway with funding from the Canadian Institutes of Health Research. The primary endpoint will be
five-year graft patency determined by x-ray angiography. In the follow-up study, we will use the more stringent measure of perfect graft patency (i.e. presence/absence of TIMI III flow) to definitively determine if the radial artery is a superior conduit. In a separate sub-study, also funded by the Canadian Institutes of Health Research, we will also gather blood samples on the patients enrolled in the five-year phase of the Radial Artery Patency Study. We aim to determine if biochemical markers including emerging inflammatory mediators (c-reactive protein, interleukins) and specific gene polymorphisms related to atherosclerosis, systemic inflammation and drug response (pharmaco-genetic interaction) will affect graft patency.

8.4 Conclusion

In summary, intraoperative graft patency assessment with ICG angiography and radial artery grafting appear to be superior techniques, which, when applied in the operating room, will lead to improved outcomes and their use is encouraged. In the future, one can imagine a minimally invasive procedure performed through small keyholes with multiple arterial conduits, robotic telemanipulation, automatic anastomotic connectors and full image guidance. The techniques and technologies studied in this thesis represent a step towards this ideal.
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