

A randomized comparison of intraoperative indocyanine green angiography and transit-time flow measurement to detect technical errors in coronary bypass grafts

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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 and indocyanine green fluorescent-dye graft angiography.

Methods: Patients undergoing isolated coronary artery bypass grafting with no contraindications for postoperative angiography were enrolled in the study. Patients were randomly assigned to be evaluated with either indocyanine green angiography (Novadaq Spy angiography system; Novadaq Technologies Inc, Concord, Ontario, Canada) and then transit-time ultrasonic flow measurement (Medtronic Medi-Stim Butterfly Flowmeter TTF measurement system; Medtronic Inc, Minneapolis, Minn) or transit-time flow then indocyanine green angiography. Patients underwent x-ray angiography on postoperative day 4. The primary end point 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 greater than 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 greater than 50% stenosis or occlusion by the reference standard. The sensitivity and specificity of indocyanine green angiography to detect greater than 50% stenosis or occlusion was 83.3% and 100%, respectively. The sensitivity and specificity of transit-time ultrasonic flow measurement to detect greater than 50% stenosis or occlusion was 25% and 98.4%, respectively. The *P* value for the overall comparison of sensitivity and specificity between indocyanine green angiography and transit-time flow ultrasonography was .011. The difference between sensitivity for indocyanine green angiography and transit-time flow measurement was 58% with a 95% confidence interval of 30% to 86%, *P* = .023.

Conclusion: Indocyanine green angiography provides better diagnostic accuracy for detecting clinically significant graft errors than does transit-time ultrasound flow measurement.

The immediate and long-term success of coronary surgery is dependent on the construction of a technically perfect anastomosis with a high-quality conduit to an appropriate target coronary vessel. Significant advances in medical therapy including early postoperative aspirin administration and increased use of arterial grafting have improved early and late graft patency. However, modern coronary bypass series continue to report perioperative graft occlusions rates between 4% and 12%.¹⁻⁴ These very early graft failures have been predominantly

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Abbreviations and Acronyms

ICG	= indocyanine green
LAD	= left anterior descending coronary artery
LITA	= left internal thoracic artery
RITA	= right internal thoracic artery
TIMI	= Thrombolysis In Myocardial Infarction
TTF	= transit-time flow

ascribed to technical problems at graft anastomosis sites and may be correctable if recognized intraoperatively.

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 (TTF) measurement has recently become a commonly used method of intraoperative 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 nonocclusive stenoses.⁵ After promising phase I clinical investigations with a novel method of intraoperative angiography using the fluorescent dye indocyanine green (ICG),^{6,7} 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.

Methods**Study Design**

The study was a prospective clinical trial comparing of the efficacy of two intraoperative diagnostic imaging modalities, ICG angiography and TTF measurements, using a within-patient randomized design. The primary objective of this study was to compare the sensitivity and specificity of ICG angiography versus TTF to detect technical problems in coronary artery bypass grafts using x-ray coronary angiography as the reference standard. Ancillary end points 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. They included 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 an allergy to ICG 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 patients with severe peripheral or carotid vascular disease, allergy to contrast dye, obligatory anticoagulation, or renal failure with a serum creatinine level greater than 150 $\mu\text{mol/L}$. 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 postoperative period. To reduce patient and vessel selection biases inherent to patency studies, all enrolled patients underwent intraoperative patency assessment with both ICG angiography and TTF. 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 was randomly assigned to be revealed to the surgeon first, with the opposing method being revealed second, that is, 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 4 to 6.

Intraoperative patency assessment. ICG angiograms were performed on all grafts using the Novadaq Spy imaging system (Novadaq Technologies 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.⁶

Visual assessment of the intraoperative angiogram was 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 Thrombolysis In Myocardial Infarction (TIMI) III flow characteristics; (2) *abnormal* = patent, with greater than 50% stenosis at any location in the graft, proximal or distal anastomosis, or immediate 1 cm of target vessel, or poor flow characteristics (non-TIMI III flow); or (3) *occluded*.

TTF was also performed on the same grafts using the Medi-Stim Butterfly Flowmeter TTF measurement system (Medtronic Inc, Minneapolis, Minn). An appropriate sized ultrasound probe (2-4 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 before chest closure and acceptable contact between the probe and the graft (acoustic coupling index > 50%). Grafts were characterized as normal, abnormal, or occluded. A graft was considered to be *normal* if all three of the following transit-time patency criteria were present: greater than 50% diastolic flow fraction, a pulsatility index of less than 5, and a mean flow of greater than 10 mL/min. Grafts were deemed *abnormal* if any two of the following criteria were present: less than 50% diastolic flow

fraction, a pulsatility index of greater than 5, or a mean flow less than 10 mL/min.⁸ 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 because 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 nonintervention for abnormal grafts was recorded by the operating surgeon. Grafts that 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 325 mg of aspirin daily starting 6 hours postoperatively, and this was continued indefinitely. In case of aspirin intolerance or allergy, antithrombotic therapy was individualized according to 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.⁹

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 postoperative 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 laboratory 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 postoperative day. All postoperative angiography was performed via the femoral artery approach. Two orthogonal angiographic views of each graft were performed. All x-ray angiograms underwent a 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.

End point assessment. For the reference standard x-ray angiography, grafts were classified as follows: (1) *normal* if they had no stenosis greater than 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 greater than 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 end point 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 (pathologic 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.¹⁰ 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 be 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 to be abnormal or occluded.

When a graft was revised in the operating room based in ICG angiography or TTF, the postoperative x-ray angiogram could not assess the validity of the operative finding since revision took place before x-ray angiography. 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 (ie, purse-stringing, twisting, occlusive stitch, dissection), 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 examination was performed.

Data Management and Statistical Methods

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

The primary comparison of the overall difference in sensitivity and specificity between the two techniques was performed with an extended McNemar test for paired data.¹¹ 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 (ie, 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 end point, 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% inpatient correlation. To account for inpatient correlation, a correction factor of 10% correlation was applied.¹² On the basis of our institutional average of 3.1 grafts per patient, this meant 53 patients were needed to undergo the intraoperative studies and postoperative x-ray angiography. Given the invasive nature of the postoperative angiogram, we anticipated that 50% of randomized patients would be either ineligible or unwilling to participate in postoperative x-ray angiography. Hence, a total of 106 patients

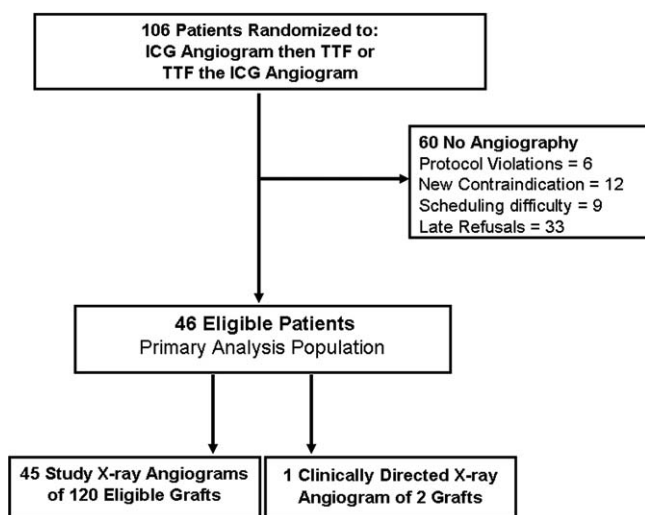


Figure 1. Trial summary. *ICG*, indocyanine green.

were intended to be recruited in this study. Individual comparisons of sensitivity and specificity were performed with the McNemar test for paired proportional data. Positive and negative predictive values were calculated according to standard methods and compared with the Fisher exact test.

Results

Patients

Between February 2004 and March 2005, 106 patients were enrolled. A trial summary is presented in Figure 1. Table 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 nonsignificant trend toward better preoperative New York Heart Association functional status among patients undergoing x-ray angiography. No other differences between groups approached statistical significance.

Operative Data

Operative data are presented in Table 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 postoperative x-ray angiography. Protocol violations occurred in 6 patients: 4 patients did not receive complete TTF assessment because of surgeon concern about damaging arterial grafts during skeletonization of a small part of the pedicle needed to make contact with the TTF ultrasound probe (6 arterial grafts were not studied in these patients), and 2 patients were withdrawn from the study after randomization because of 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 a 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 3 grafts constructed and studied intraoperatively with ICG angiography and TTF. One graft (right internal thoracic artery–left anterior descending coronary

TABLE 1. Clinical characteristics of all participants and those who underwent x-ray angiography

	All patients (n = 106)	Patients with angiography (n = 46)
Age, $y \pm SD$	65.5 \pm 10.3	65.1 \pm 10.1
Nonelective surgery, No. (%)	35 (33.0)	12 (26%)
Previous MI, No. (%)	54 (50.9)	22 (47.8)
Female, No. (%)	14 (13.2)	6 (13.0)
NYHA functional class III or IV, No. (%)	58 (54.7)	20 (43.5)*
Diabetes, No. (%)	35 (33.0)	15 (32.6)
Hypertension, No. (%)	66 (65.1)	29 (63.0)
Dyslipidemia, No. (%)	90 (84.9)	40 (87.0)
Smoking history, No. (%)	61 (57.5)	24 (52.2)
Preoperative creatinine, No. (%)	87.7 \pm 20.7	83.1 \pm 17.2
Peripheral vascular disease, No. (%)	10 (9.4)	3 (6.5)
COPD, No. (%)	6 (5.7)	2 (4.3)
LVEF < 35%, No. (%)	19 (17.9)	10 (21.7)
No. of diseased vessels 1/2/3, No. (%)	1/26/79 (0.9/24.5/74.5)	0/12/34 (0/26.0/74.0)

SD, Standard deviation; MI, myocardial infarction; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; LVEF, estimated global left ventricular ejection fraction. * $P = .07$ for comparison between all patients and those undergoing angiography.

TABLE 2. Operative data for all participants and those who underwent x-ray angiography

	All patients (n = 106)	Patients with angiography (n = 46)
No. of bypass grafts, mean ± SD	3.2 ± 0.8	3.0 ± 0.9
No. of arterial grafts, mean ± SD	1.9 ± 0.8	2.0 ± 0.7
Off-pump, No. (%)	2 (1.9)	1 (2.2)
Operating room time, mean ± SD	278.6 ± 65.4	282.9 ± 75.8
CPB time, mean ± SD	126.4 ± 34.2	127.9 ± 40.7
Crossclamp time, mean ± SD	106.4 ± 31.1	107.6 ± 35.9
TTF, No. (%)		
Normal	325 (97.6)*	134 (96.4)
Abnormal	6 (1.8)	3 (2.2)
Occluded	2 (0.6)	2 (1.4)
ICG, No. (%)		
Normal	328 (96.8)	129 (92.8)
Abnormal	9 (2.6)	8 (5.8)
Occluded	2 (0.6)	2 (1.4)

SD, Standard deviation; CPB, cardiopulmonary bypass; TTF, transit-time flowmetry; ICG, indocyanine green angiography. *Six arterial grafts in 4 patients were not studied with TTF.

artery [RITA-LAD]) was revised in the operating room because of excessive bleeding. This graft was not reimaged with ICG angiography or TTF and is therefore ineligible for the analysis. The graft was deemed to be 99% occluded at repeat angiography, and angioplasty was performed. Information regarding the other 2 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 the cardiac catheterization laboratory in 9 patients, and withdrawal of consent for the x-ray angiogram in 33 patients. No patients had 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 3. Twelve of 139 (8.6%) grafts were 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 of 49 (10.2%) were totally occluded. By reference standard, abnormal grafts were observed in 3 of 46 (6.5%) left internal thoracic artery (LITA) grafts, 0 of 12 (0%) RITA grafts, 2 of 32 (6.3%) radial artery grafts, and 2 of 49 (4.1%) saphenous vein grafts.

The sensitivity and specificity of ICG angiography to detect abnormal/occluded grafts were 83% and 100%, re-

spectively. The sensitivity and specificity of TTF to detect abnormal/occluded grafts were 25% and 98.4%, respectively. The *P* value for the primary end point of the overall comparison of sensitivity and specificity between ICG angiography and TTF was .011 (see Tables 4 and 5). The difference between sensitivity for ICG angiography and TTF was 58% with a 95% confidence interval of 30% to 86%, *P* = .023. The difference between specificity for ICG angiography and TTF was 1.8% with a 95% confidence interval of -0.3% to 3.9%, *P* = .47. The positive predictive value was 100% for ICG angiography and 60% for TTF, *P* = .68. The negative predictive value was 98.4% for ICG angiography and 93.2% for TTF, *P* = .79.

False negatives. One vein graft found to be totally occluded on postoperative angiography had a normal ICG angiogram and normal TTF measurements (mean flow 56 mL/min, pulsatility index 2.0, diastolic flow fraction 69%). For ICG angiography, there was 1 additional false negative case: a diffuse 80% narrowing of a distal radial artery graft in which the graft lumen was not well visualized intraoperatively owing to a thick graft pedicle. For TTF, 8 additional false negatives occurred. These included 3 abnormal LITA-LAD anastomoses (including one 60% lesion in the immediate distal vessel past the graft-coronary anastomosis), 1 abnormal diffuse 80% distal narrowing of a radial artery graft, 1 abnormal distal radial artery–obtuse marginal anastomosis, 1 abnormal vein graft, and 2 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 (ie, false positives). These included a LITA-LAD graft with a mean flow of 6 mL/min, 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 ± 16.3 mL/min in grafts deemed normal by the reference standard, 24.4 ± 8.7 mL/min in grafts deemed abnormal by the reference standard, and 16.4 ± 23.0 mL/min in grafts determined to be occluded by reference standard (overall analysis of variance *P* = .07). This included 2 grafts with intraoperative mean flows of 0 mL/min that were both corrected at the time of operation. Mean intraoperative TTF-derived pulsatility index was 2.8 ± 1.4 in grafts deemed normal by x-ray angiography, 3.0 ± 1.1 in grafts deemed abnormal by x-ray angiography, and 4.6 ± 3.2 in occluded grafts (overall analysis of variance *P* = .1), including 2 grafts with no flow and undefined pulsatility indices. Mean intraoperative TTF-derived diastolic flow fraction was 57.3 ± 19.3 in grafts deemed normal by x-ray angiography, 58.4 ± 8.1 in grafts deemed abnormal

TABLE 3. Graft patency data for ICG angiography, TTF and reference standard x-ray angiography or pathologic graft assessment stratified by graft type

	Graft type				Total
	LITA	RITA	Radial	SVG	
Total grafts reviewed	46	12	32	49	139
ICG graft assessment					
Normal	43	12	31	43	129
Abnormal	3	0	1	4	8
Occluded	0	0	0	2	2
TTF graft assessment					
Normal	45	12	31	46	134
Abnormal	1	0	1	1	3
Occluded	0	0	0	2	2
Reference standard					
Normal	43	12	30	42	127
Abnormal	3	0	2	2	7
Occluded	0	0	0	5	5
True positives					
ICG	3	0	1	6	10
TTF	0	0	0	3	3
False positives					
ICG	0	0	0	0	0
TTF	1	0	1	0	2
True negatives					
ICG	43	12	30	42	127
TTF	42	12	29	42	125
False negatives					
ICG	0	0	1	1	2
TTF	3	0	2	4	9

LITA, Left internal thoracic artery; RITA, right internal thoracic artery; Radial, radial artery; SVG, saphenous vein graft; ICG, indocyanine green angiography; TTF, transit-time flowmetry.

by x-ray angiography, and 34.0 ± 32.3 in occluded grafts (overall analysis of variance $P = .03$).

Clinical Outcomes

Clinical outcomes are presented in Table 6. There were no significant differences in clinical outcomes between all enrolled patients and those who underwent x-ray angiography. The median postoperative length of stay was similar between groups. There were no perioperative deaths. Perioperative myocardial infarction occurred in 6 (5.6%) patients, including 1 patient with an abnormal LITA-LAD graft. Repeat revascularization occurred in 2 patients. In 1 patient, a LITA-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. Owing 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 revascular-

TABLE 4. Comparison of ICG angiography and TTF to detect grafts that were determined to be occluded/abnormal by pathologic or x-ray angiogram analysis (ie, sensitivity)

	ICG positive	ICG negative
TTF positive	3	0
TTF negative	7	2

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 2 graft errors. ICG, Indocyanine green angiography; TTF, transit-time flowmetry.

ization occurred in 6.6% of enrolled patients. Among the 46 patients who underwent x-ray angiography, peak serum troponin was $0.24 \pm 2.4 \mu\text{mol/L}$ among patients with normal grafts and $1.2 \pm 1.3 \mu\text{mol/L}$ among patients with abnormal/occluded grafts, $P = .17$.

Discussion

Increasing emphasis is being placed on quality assessment in cardiac surgery. Despite significant improvements in the quality of processes of care in coronary surgery over the past decade, there is still no widely accepted or broadly used technique to assess the quality of the bypass graft itself. Inasmuch as graft patency is the predominant determinant of late survival and freedom from reintervention after coronary bypass surgery, assuring technical perfection in the operating room is a current imperative. The need for intraoperative patency assessment has been highlighted by recent high-impact studies by Puskas,¹³ Khan,¹⁴ and their associates, which demonstrate there is significant surgeon-specific variation in graft patency in off-pump coronary bypass procedures. The clinical consequences of early graft failure are not benign. In a recent report, among patients with early postoperative graft failure, the 30-day mortality was over 9%.¹⁵ In the current study, peak postoperative troponin levels were greater in patients with abnormal or occluded grafts.

Among graft assessment techniques currently available, contrast dye x-ray coronary angiography remains the gold or reference standard. However, it is generally not available in the cardiac operating room because of logistical difficulties incorporating bulky equipment and safety concerns regarding contrast-induced renal insufficiency, aorto-embolic complications, and bleeding complications. Although graft patency assessment techniques such as thermal angiography, Doppler flow measurement, and electromagnetic flow measurement have been attempted in the operating room, such techniques generally do not provide high-fidelity angiographic information and have not gained implementation into routine surgical practice.¹⁶⁻²⁰

TABLE 5. Comparison of sensitivity and specificity of ICG angiography and TTF

	ICG angiography	TTF	P value
Sensitivity (TP/TP+FN)	10/12 (83.3%)	3/12 (25%)	.023*
Specificity (TN/TN+FP)	127/127 (100%)	125/127 (98.4%)	.47 *
Positive predictive value (TN/TN+FN)	10/10 (100%)	3/5 (60.0%)	.68
Negative predictive value	127/129 (98.4%)	125/134 (93.2%)	.79

ICG, Indocyanine green angiography; TTF, transit-time flowmetry; TP, true positive; TN, true negative; FP, false positive; FN, false negative. *Overall $P = .011$ from extended McNemar test for simultaneous comparison of sensitivity and specificity.

With the rise of off-pump coronary surgery, TTF 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 dependent 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.²¹

ICG 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.⁶

This trial was designed to determine the superior method of verifying intraoperative graft patency. Our investigation

revealed that ICG angiography had better diagnostic accuracy than TTF, with x-ray angiography used as the reference standard. In total, 12 of 139 (8.6%) grafts studied by the reference standard were abnormal or occluded in this study. ICG angiography correctly identified 83% of these abnormal/occluded grafts whereas TTF identified only 25%. ICG angiography correctly identified 87.5% of 8 grafts with nonocclusive (>50%) stenoses whereas TTF was not able to identify any of these abnormal grafts. Among 5 grafts that were determined to be totally occluded by the reference standard, ICG angiography identified 80% whereas 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.⁵ In off-pump cases, some authors⁸ have recommended that TTF measurements be performed with a proximal snare in place. We did not snare proximally as most cases were performed on-pump, and this technique may 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,

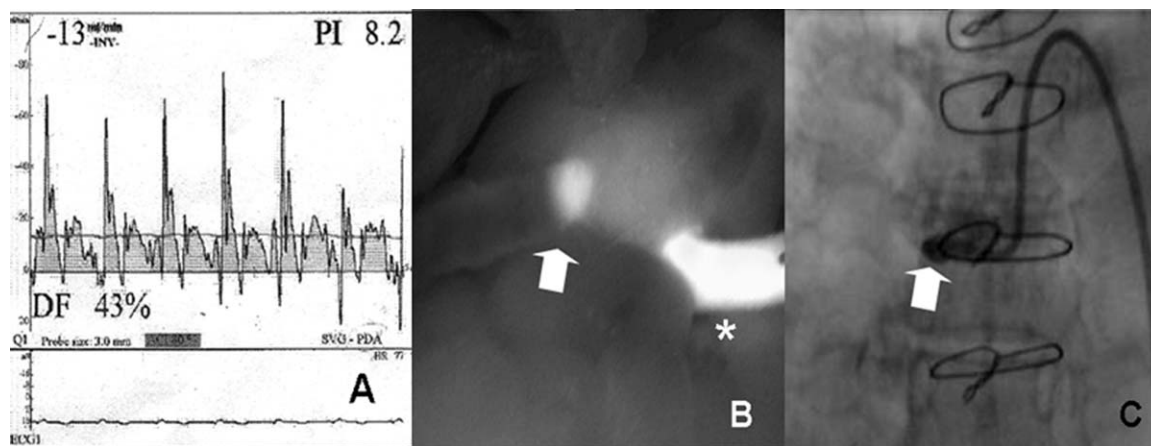


Figure 2. Representative TTF assessment (A), ICG angiogram (B), and x-ray angiogram (C) images of an occluded saphenous vein graft to the posterior descending coronary artery. TTF measurements were grossly abnormal (pulsatility index > 5 and diastolic flow fraction 43%). ICG angiography and x-ray angiography show an occluded vein stump (white arrows). A normally filling proximal vein graft to an obtuse marginal branch is seen in the ICG angiogram (asterisk). TTF, transit-time ultrasound flow; ICG, indocyanine green.

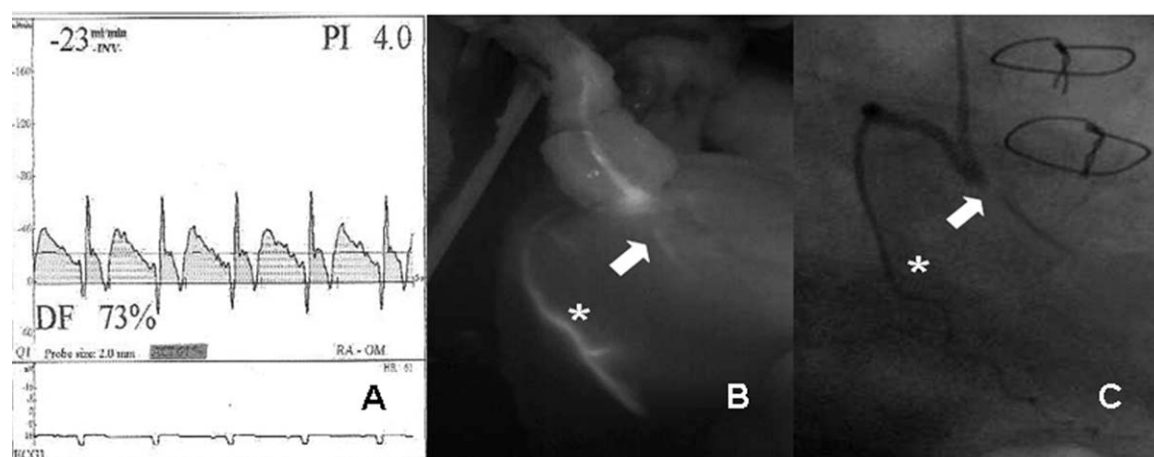


Figure 3. Representative TTF assessment (A), ICG angiogram (B), and x-ray angiogram (C) images of a near-total occlusion of a radial artery graft–first obtuse marginal (RA-OM) branch distal anastomosis. A near-total occlusion is visualized at the distal portion of the anastomosis (white arrows) on ICG 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 a 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 (PI) = 4.0; 73% diastolic flow fraction (DF); ECG, electrocardiogram; TTF, transit-time ultrasound flow; ICG, indocyanine green.

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 used in patients who were expected to have postoperative angiography.

The patency characteristics of one graft appeared to have changed between the intraoperative studies and postoperative day 4 angiography. In this saphenous vein graft, both TTF measurement and ICG angiography showed a completely normally functioning graft that was totally occluded at the time of day 4 angiography. The cause of this occlu-

sion was uncertain but may have been due to graft kinking resulting from closure of the pericardium or a late graft thrombosis or embolic phenomenon. There was no biochemical or electrocardiographic evidence of postoperative myocardial infarction in this patient.

Although 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 postoperative intravenous nitroglycerin 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 thoracic artery or saphenous vein grafts.^{6,22} 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 4 patients enrolled in this trial, the operating surgeon did not use the TTF probe because of concerns that placing it around an arterial graft would damage 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.

TABLE 6. Thirty-day clinical outcomes

	All patients	Patients with angiography
Median length of stay, d (IQR)	7 (6-11)	7 (7-9)
Mean length of stay, d ± SD	10.6 ± 10.1	8.8 ± 5.5
Death, No. (%)	0	0
Nonfatal MI,* No. (%)	6 (5.6)	2 (4.3)
Peak troponin (μmol/L), mean ± SD	0.3 ± 2.3	0.4 ± 2.1
Repeat coronary surgery, No. (%)	0	0
Coronary angioplasty, No. (%)	2 (1.9)	2 (4.3)
Composite end point† No. (%)	7 (6.6)	3 (6.5)

IQR, Interquartile range. *Myocardial infarction (MI) = persistent new pathologic Q-waves on the postoperative electrocardiogram or characteristic ST-T segment changes with positive enzymes. †Composite end point = death, nonfatal MI, or any repeat revascularization.

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

In conclusion, ICG angiography had superior diagnostic accuracy to TTF flow measurement. This difference was observed primarily in nonocclusive but clinically significant stenoses as opposed to total occlusions. In the context of historical and contemporary graft patency studies, which have shown that 4% to 12% of bypass grafts fail in the early postoperative period, intraoperative ICG angiography will likely be able to identify most of these lesions before chest closure. This potential effect on early graft patency is greater than that of well-established methods of improving early or 1-year graft patency, including perioperative aspirin use and antilipid medications.^{23,24}

Intraoperative patency assessment with ICG angiography represents a significant advance in coronary bypass quality assurance.

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Appendix

Participating Surgeons: Dr Stephen E. Fremes, Dr George T. Christakis, Dr Bernard S. Goldman, Dr Gideon N. Cohen, Dr Stacy O'Blenes (Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario, Canada); Dr Robert J. Cusimano (Toronto General Hospital, Toronto, Ontario, Canada)

Participating Cardiologists: Dr Eric Cohen, Dr Christopher Morgan, Dr Mina Madan, Dr Sam Radhakrishnan, Dr James Dubbin, Dr Michael-Bentley Taylor, Dr Bruce Lubelsky, Dr Alexander Dick, Dr Sal Naqvi (Sunnybrook and Women's College Health Sciences Centre)

Study Coordinator: Randi Feder-Elituv (Sunnybrook and Women's College Health Sciences Centre)

Cardiac catheterization laboratory coordinators: Sherri Mifsud, Connie Cristavo (Sunnybrook and Women's College Health Sciences Centre)

Statistical Consultation: Dr Alexander Kiss, Marko Katic (Institute for Clinical Evaluative Sciences)

Discussion

Dr Robert C. Robbins (Stanford, Calif). This system was developed by a Canadian company and just received Food and Drug

Administration approval in the States. We actually did the first couple of cases at Stanford.

I am sure there is a learning curve, but how long does it take to get proficient enough to get these kinds of images that will really help you? Does the surgeon always read the angiograms or do you have someone else, a cardiologist, come in and read the angiograms?

Dr Desai. Our surgeon reads the angiogram. This study was performed after pilot studies on 120 patients looking at about 348 angiograms. There is a modest learning curve in being able to identify nonocclusive lesions.

First of all, it is important for surgeons to be aware that in fact more grafts have technical errors than they are usually willing to acknowledge or appreciate. We now have a library of x-ray angiograms and corresponding ICG angiograms that we use for teaching purposes.

Dr Beat H. Walpoth (*Geneva, Switzerland*). I do not agree completely with what you have said. Of course, for a surgeon it is always nice to see the morphologic features of the coronary bypass graft, anastomosis, and the runoff in the distal native vessel, of which your method gives some indication. However, it is only monoplane and the quality cannot be compared with other imaging techniques for assessment of the anastomosis. I think the TTF measurement is a very good method to detect a critical stenosis that will have clinical relevance. Even so, there is a debate regarding the lower cutoff value and the curve shape. The curve shape, especially the systolic-diastolic filling pattern, is changing according to the location where the measuring probe is applied on the bypass graft. If you make a proximal measurement, the signal will mainly be systolic, whereas if you measure distally, the signal will mainly be diastolic. Could you comment on the fact that you applied different failure criteria for the flow and morphologic measuring techniques that you applied in this study?

Dr Desai. In general, our TTF measurements were taken more distally along the graft, and you are absolutely right, we did see a gradient in terms of the diagnostic accuracy of the test. When we looked at occluded grafts, that is, grafts that were proven to be occluded by x-ray angiogram or positive findings at surgical revision, we found that TTF performed much better than it did looking at grafts that had a 60% or 70% or 80% stenosis. In those situations, TTF was not able to pick up any of the lesions.

Dr John G. Byrne (*Nashville, Tenn*). You mentioned that the pedicled grafts are more difficult to image. Can you expand on that?

Dr Desai. The technique is a line-of-sight technique, and there is a near infrared laser that illuminates the dye when it is inside the

vessel lumen. For a thick pedicled graft, the light generally will penetrate through the pedicle into the lumen of the graft and excite the dye. When the light comes back out of the graft, it is dispersed by the pedicle tissue. You do not get a clear depiction of the lumen. You get a more hazy image.

Dr Byrne. A second question: Do you have to cannulate the thoracic pedicles separately, do you just inject them in the pump, or what do you do?

Dr Desai. You can inject in the pump and you can inject in a central venous line. If you are on or off pump, you can inject straight down the graft if it is a free vessel.

Dr Mark J. Krasna (*Baltimore, Md*). Have you had experience in your institution with the thermal imaging technique, and how does that compare?

Dr Desai. We have not used thermal angiography. I know that there is a new method of thermal angiography that has become available recently, but to my knowledge no validation studies have been done with that technique yet.

Dr Krasna. This is really an elegant prospective randomized trial. Of course, it would have been even more elegant if all patients had undergone angiography. Since 54 of the 94 patients actually did not have standard x-ray angiography, can you comment again about the reasons they did not and whether you think it would have made a difference given your statistics?

Dr Desai. As stated in my presentation, the majority of cases in which standard x-ray angiography was not done were due to patient refusal. There were also a group of patients who had a new medical contraindication to x-ray angiography, which generally meant arrhythmias or need for anticoagulation. There were several instances in which the patient was stable, willing, and capable of undergoing the angiogram, but the catheterization laboratory in our hospital was not able to provide access in a timely fashion.

Dr Krasna. Do you think it would have changed your data, changed your results?

Dr Desai. Because the comparison was a paired comparison, I think it would not change the differential between intraoperative angiography and TTF measurement. The actual point estimate for the number of graft errors may change.

Dr Robert C. Robbins (*Stanford, Calif*). You alluded to it, and I tried to find it in your manuscript: How many grafts were actually revised out of the 154?

Dr Desai. Five graft revisions were attempted. Some grafts were not repairable owing to poor distal targets.