Skeletonized Internal Thoracic Artery Harvest Reduces Pain and Dysesthesia and Improves Sternal Perfusion After Coronary Artery Bypass Surgery
A Randomized, Double-Blind, Within-Patient Comparison

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Background—Observational studies suggest that skeletonization of the internal thoracic artery (ITA) can improve conduit flow and length and reduce deep sternal infections and postoperative pain. We performed a randomized, double-blind, within-patient comparison of skeletonized and nonskeletonized ITAs in patients undergoing coronary surgery.

Methods and Results—Patients (n=48) undergoing bilateral ITA harvest were randomized to receive 1 skeletonized and 1 nonskeletonized ITA. Intraoperatively, ITA flow was assessed directly and with a Doppler flow probe before and after topical application of papaverine. ITA harvest time and conduit length were recorded. A blinded assessment of pain (visual analog scale) and dysesthesia (physical examination) was performed at discharge, at 2 weeks, and at a 3-month follow-up. Sternal perfusion was assessed with nuclear imaging (n=7). Skeletonization required longer ITA harvest times (27±1 versus 24±1 minutes; P=0.04). There was a trend toward increased ITA length in the skeletonized group (18.2±0.3 versus 17.7±0.3 cm; P=0.09). In situ ITA flow was lower in skeletonized arteries (7.4±0.9 versus 10.1±1.0 mL/min; P=0.01) and increased significantly after ITA division and papaverine application. Postanastomotic flows were similar between groups. Skeletonization was associated with decreased pain at the 3-month follow-up and a reduction in major sensory deficits at the 4-week and 3-month (17% versus 50%; P=0.002) follow-ups. Baseline adjusted sternal perfusion was significantly greater by 17±6% (P=0.03) on the skeletonized side.

Conclusions—Skeletonization results in reduced postoperative pain and dysesthesia and increased sternal perfusion at follow-up but does not produce increased conduit flow. ITA skeletonization may be a strategy for reducing morbidity after CABG. (Circulation. 2006;114:766-773.)

Key Words: coronary artery bypass ■ mammary arteries ■ randomized controlled trials ■ tissue and organ harvesting ■ pain, postoperative

Coronary artery bypass surgery remains the gold standard for the treatment of multivessel and left main coronary disease.1 The use of the internal thoracic arteries (ITAs) as bypass conduits has been associated with improved long-term outcome after CABG.2,3 Despite these long-term benefits, certain characteristics of the ITAs limit their use in particular settings. The ITAs can be prone to vasospasm and hypoperfusion in the early postoperative period, particularly in the presence of vasoactive medications.4,5 Harvest of the ITAs is associated with impairment in sternal perfusion6 and increased deep sternal wound infections,7 particularly in diabetic patients receiving bilateral ITAs. The length of usable conduit available can be limited in the setting of sequential grafting. In addition, ITA harvest has been associated with increased and persistent postoperative pain.8–10

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efits of skeletonization include increased flow\textsuperscript{14} and length,\textsuperscript{12} decreased sternal infection rates,\textsuperscript{15,16} and reduced pain.\textsuperscript{17} However, these assertions are supported primarily by nonrandomized, observational studies. Not surprisingly, there is considerable debate about the optimal harvesting technique for the ITA.

The aim of the present study was to determine whether skeletonization of the ITA leads to differences in ITA flow, length, sternal perfusion, and postoperative pain and dysesthesia.

Methods

We conducted a prospective, randomized, double-blind, within-patient study in which patients undergoing bilateral ITA harvest received 1 skeletonized and 1 nonskeletonized ITA. The side that received the skeletonized ITA was randomly assigned. This design eliminates the variation resulting from interpatient differences by using patients as their own controls and therefore sensitively captures the differences attributable to harvesting technique.

Patient Population

This single-center study was approved by the Human Research Ethics Board of the University of Ottawa Heart Institute, and written informed consent was obtained from all participating subjects. From September 2003 to September 2005, patients undergoing nonemergent, isolated CABG requiring bilateral ITA harvest by 2 participating surgeons were screened for eligibility. Exclusion criteria included lack of fluency in English or French, inability to return for follow-up visits, participation in another research study, and planned use of the ITA for sequential grafting.

Intraoperative Protocol

The protocol for this study has been previously described.\textsuperscript{18} Patients were randomized in the operating room at the time of sternotomy by opening an opaque envelope containing a preassigned, computer-generated random sequence. All patients received 1 skeletonized and 1 nonskeletonized ITA, and the side (left versus right) that received the skeletonization and the order in which the conduits were harvested were randomly assigned.

Start and end times of dissection were recorded for each conduit. The ITA was harvested using a combination of electrocautery (coagulation power, 18 W; fulgurate setting) and scissors, and hemoclips were used to ligate ITA branches. The length of the harvested ITA was measured in situ from the first rib to ITA bifurcation in a standardized fashion as follows: After the conduit had been fully dissected from the top of the first rib to the bifurcation, the middle portion was encircled by a silk suture, and uniform tension was applied to the 2 ends of the suture by attaching a Kelly forceps that was allowed to hang by gravity over the opposite side of the sternum. The 2 distances from this middle portion to the top of the first rib and to the bifurcation were then measured and added to obtain the total conduit length.

ITA flow was measured on 4 separate occasions. In situ ITA flow was measured 3 to 5 minutes after harvest with an appropriately sized Doppler flow probe (Transonics Inc, Binghamton, NY). The same probe was used for both ITAs to minimize variability and measurement error. After both ITAs were harvested, systemic heparin was administered, and the ITAs were divided distally. Direct blood flow from each ITA was quantified on distal division by measuring the amount of blood filling a calibrated cup over 15 seconds. The ITAs were then treated with topically applied papaverine, a phosphodiesterase inhibitor, at a concentration of 3.25 mg/mL for 5 minutes, and direct flow was measured again. The patient then underwent CABG with or without the use of cardiopulmonary bypass. The final flow measurement was performed with the Doppler flow probe after all anastomoses had been completed. Mean arterial pressure was recorded at each flow measurement.

Assessment of Sternal Perfusion

A subgroup of patients (n = 7) were randomly chosen to undergo assessment of sternal perfusion. Before and after the operation, each patient underwent a SPECT bone scan of the chest to evaluate sternal vascularity. Each patient received 925 MBq technetium-99m methylene diphosphonate intravenously for each study. The images were acquired with a dual-head gamma camera (ECAM, Siemens, New York City, NY); low-energy, high-sensitivity collimators; and a 20% energy window centered at 140 KeV. For SPECT studies, 32 projections, 20 seconds for each camera head over a 180° arc, were acquired in a 128×128 matrix. Images were reconstructed with the iterative reconstruction algorithm OSEM (Hermes Medical System). The reconstructed coronal images were realigned along the sternal axis, and 3 slices (each 3.6 mm thick) were summed to generate the final image for quantification.

The quantitative analysis was performed by a nuclear medicine physician blinded to patients’ clinical presentations and operative status. A rectangular region of interest was drawn manually over the right hemisternum. A mirror image of an equivalent region of interest, with the same number of pixels, was placed on the left hemisternum. In addition, the sternum was divided into upper, middle, and lower regions equally, and a region of interest with an equal number of pixels was placed in each region. The total counts of each region on the skeletonized hemisternum were compared with that of the nonskeletonized hemisternum after adjustment for baseline (preoperative) values.

Assessment of Postoperative Pain and Dysesthesia

Assessments of chest wall pain and dysesthesia were performed by a blinded observer before discharge (4 to 6 days postoperatively) and at 4 weeks and 3 months postoperatively. A questionnaire designed to assess differences in pain between the left and right sides was administered to patients, and the degree of pain was quantified with a 100-mm visual analog scale (VAS; 0 = no pain, 100 = worst pain). To assess sensory deficits, we used 3 different sensory modalities. Deficits in light touch, pinprick sensation, and cold temperature were assessed and mapped out on a grid by systematically testing the entire anterior chest wall on both sides of the entire length of the midline skin incision. Consistent with a previously reported definition of intercostal nerve damage by Mailis et al.,\textsuperscript{19} a major sensory deficit was defined as the presence of a deficit in response to ≥2 sensory modalities tested that occurred in an intercostal nerve distribution and measuring at least 50 cm² (approximately the area of the palm of the hand).

Safety End Points and Data Collection

Safety end points monitored included ITA harvest time, gross ITA injury, sternal fractures, chest tube drainage, need for reoperation for bleeding, and superficial or deep sternal wound infections. Information on baseline characteristics, intraoperative variables, and postoperative outcomes was collected prospectively.

Statistical Analysis and Sample Size Calculations

Paired analyses were conducted for all end points. Continuous variables were analyzed with ANOVA, adjusting for the side receiving the skeletonized harvest. Differences in conduit flow (milliliters per minute), length (centimeters), sternal perfusion (counts per pixel), chest wall pain (VAS score), and area of chest wall dysesthesia (square centimeters) were analyzed with these methods. In addition, chest wall pain and chest wall dysesthesia also were dichotomized and analyzed as binary end points with McNemar’s test. Continuous outcomes are presented as mean±SEM. All statistical analyses were conducted with SAS version 9.1 (SAS Institute, Cary, NC).

The primary outcome for sample size calculation was direct ITA flow at the second measurement before papaverine application. To detect an absolute difference of 8 mL/min between skeletonized and nonskeletonized ITAs (30% increase in flow) with the assumption of a mean flow of 26.4±16.1 mL/min in the nonskeletonized group\textsuperscript{14} at a 2-sided α level of 0.05 and 90% power, 45 pairs of ITAs were
required. Forty-eight patients were recruited for this study. No interim analyses were conducted.

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Results

A total of 601 patients were screened for eligibility. Of the 78 patients who met the inclusion and exclusion criteria, 48 were included in the study (Figure 1). One patient was excluded because of a protocol violation. All other patients underwent the experimental protocol. Preoperative, intraoperative, and postoperative data for the study patients are shown in the Table.

Interaction terms between treatment (ie, skeletonized versus nonskeletoned harvest) and side (ie, left versus right) were evaluated for all outcome measures and found to be nonsignificant, suggesting that the effect of treatment was similar between sides.

Intraoperative Outcomes

There were no gross ITA injuries during harvest. ITA harvest time was slightly longer for skeletonized vessels (27±1 versus 24±1 minute; paired difference, -2.7±1.3 minutes; P=0.04). Skeletonized ITAs demonstrated a trend toward increased length (18.2±0.3 versus 17.7±0.3 cm; paired difference, -0.47±0.26 cm; P=0.09). ITA flow data are depicted in Figure 2. Immediately after harvest, flow in the in situ ITA was lower in the skeletonized vessel (-5.4±2.0 mL/min; P=0.009). After distal division, ITA flow increased significantly (4- to 5-fold) and was similar in skeletonized and nonskeletoned vessels both before (P=0.36) and after (P=0.85) papaverine application. Postanastomotic flows were not significantly different in skeletonized and nonskeletoned vessels (P=0.16).

Interestingly, flow in the right ITA was consistently higher than in the left ITA before (P=0.08) and after ITA division both with (P=0.01) and without (P=0.002) papaverine treatments. However, postanastomotic flows were similar between the left and right ITAs (P=0.55), as illustrated in Figure 2B.

Sternal Perfusion

The skeletonized side demonstrated increased sternal perfusion in all but 1 patient. As shown in Figure 3, total sternal perfusion (along the entire length of the sternum) was increased on the skeletonized side (17±6% increase compared with nonskeletoned side; P=0.03). To determine the region most affected, the sternum was divided into 3 equal regions of interest. The differential increase in perfusion was most pronounced in the upper third of the sternum (24±8% increased compared with the nonskeletoned side; P=0.03). The difference in perfusion in the middle third and lower third of the sternum was not significantly different between skeletonized and nonskeletoned sides.

Chest Wall Pain and Dysesthesia

Patients reported decreasing pain along the midline incision over time (VAS scores, 2.59±0.29, 1.47±0.25, and 0.79±0.17 at discharge and 4 weeks and 3 months postoperatively). There were no significant differences in VAS scores between skeletonized and nonskeletonized sides at discharge (P=0.30) and at the 4-week follow-up (P=0.26). However, at the 3-month follow-up, VAS pain scores were significantly lower for the skeletonized side (P=0.05; Figure 4A). Furthermore, as depicted in Figure 4B, more patients reported increased pain on the nonskeletonized side at 3 months (McNemar’s test, P=0.04). Three patients (6%) reported being completely pain free at discharge compared with 6 patients (15%) at 4 weeks and 19 (40%) at the 3-month
follow-up. At discharge, 88% of all patients reported using analgesic medications compared with 59% at 4 weeks and 15% at 3 months.

Figure 5 summarizes the data on sensory abnormalities, and Figure 6 depicts a representative image of 1 patient’s sensory abnormalities to pinprick sensation depicted on the grid used to assess sensory deficits. The area of dysesthesia improved over time, but significant sensory deficits to pinprick and temperature persisted up to 3 months. The nonskeletonized sides had a significantly larger area of chest wall

Figure 2. Intraoperative flow measurements performed in situ, after distal division, after topical papaverine application, and after distal anastomoses in (A) skeletonized versus nonskeletonized ITAs and (B) left versus right ITAs (*p<0.009; †p<0.002; ‡p=0.01).

Figure 3. A, Representative SPECT Image of postoperative sternal perfusion in a patient who received a left skeletonized and a right nonskeletonized ITA. Differences in sternal perfusion are discernible in the manubrium and middle third of the sternum. B, Total sternal perfusion was higher on the skeletonized side (17±6%; *p=0.034), and differences in perfusion between the skeletonized and nonskeletonized sides were most significant in the upper third of the sternum (24±8%; †p=0.030).
dysesthesia in response to all 3 sensory modalities at all time points (all \( P < 0.03 \)), except for light touch assessed at discharge, which was not significantly different between the 2 sides (\( P = 0.40 \)). The occurrence of major sensory deficits (defined as deficits measuring at least 50 cm\(^2\) in ≥2 sensory modalities) was significantly greater on the nonskeletonized side at 4 weeks (\( P = 0.004 \)) and 3 months (\( P = 0.002 \)). Overall, differences in sensory abnormalities were present at discharge but were accentuated during follow-up.

**Discussion**

Despite the excellent long-term results of surgical coronary revascularization with the ITA, certain characteristics of this conduit and the manner in which it is harvested can lead to postoperative morbidity. In this study, skeletonization did not result in significant differences in ITA injury and intraoperative ITA flow but demonstrated a trend toward increased conduit length. We observed a significant reduction in postoperative pain on the skeletonized side and pronounced reductions in the incidence of major sensory deficits and the total area of dysesthesia. Finally, increased perfusion of the sternum was demonstrated on the skeletonized side, which may lead to a reduction in deep sternal wound infections. In summary, our results suggest that skeletonization of the ITA can reduce morbidity associated with ITA use for CABG.

A number of studies have proposed various benefits of ITA skeletonization. These include increased conduit flow, decreased deep sternal infections, and reduced postoperative pain. These assertions are supported primarily by observational studies that suffer from selection bias and residual confounding. The randomized trials in this area have evaluated sternal perfusion, vessel wall integrity, and vasoreactive profiles while studying small groups of patients. All of the randomized studies evaluated patients assigned to receiving a skeletonized or nonskeletonized left ITA. Major limitations of these randomized studies are the small sample sizes that may lead to unbalanced distribution of confounders in the 2 groups and the limited clinical relevance of the end points studied. We report the first within-patient, randomized comparison of skeletonized and nonskeletonized ITA harvest in a relatively large sample (\( n = 96 \) conduits in 48 patients) with a focus on clinically relevant early end points of ITA flow, length, postoperative pain and dysesthesia, and sternal perfusion.

Contrary to the results of previously published observational studies, we found that skeletonization did not result in increased ITA flow. Conduit flow was lower in the skeletonized vessel immediately after harvest, probably because of vasospasm resulting from closer vessel manipulation, and was similar between groups after distal division, topical papaverine application, and coronary anastomoses. There was a trend toward increased conduit length of \( \approx 0.5 \) cm in skeletonized ITAs, in contrast to previous nonrandom-
ized studies that have reported an increase up to 2.5 cm.12 The discordance between published studies and this trial may be due to variations in the skeletonization technique and vasodilator use, biases in patient selection, and other variables related to outcome that may have been unequally distributed between treatment groups in these observational comparisons. Interestingly, in our study, flow in the right ITA was greater than in the left at all time points except after anastomosis. This may be due to an anatomic difference between right and left ITAs or may be related to the patient handedness.

Previous studies have demonstrated that single and particularly bilateral ITA harvest is associated with a significant reduction in sternal perfusion.6 These defects in sternal perfusion have been shown to improve over time, but their occurrence in the perioperative period has important implications for sternal healing after surgery. Cohen et al19 have previously demonstrated the benefits of skeletonization on sternal perfusion between patients assigned to a skeletonized versus nonskeletonized left ITA harvest. We have reproduced these findings in a more robust model, eliminating interpatient variability by using within-patient comparisons. Consistent with previous reports, the manubrium is most affected by the harvesting technique.23 Although our evaluation was limited to 7 patients, these results reinforce the idea that skeletonization of the ITA can preserve blood flow to the sternum and may therefore contribute to a reduction in deep sternal wound infections, particularly in high-risk patients.

The impact of postoperative pain and dysesthesia on the quality of life and functional status of patients undergoing cardiac surgery is a relatively understudied area. Data from patients undergoing mastectomy and thoracotomy, both of which can result in chest wall pain and dysesthesia because of intercostal nerve damage, suggest that persistent pain and dysesthesia can reduce patient quality of life.24,25 The ITA syndrome, defined by Mailis and colleagues,9 is associated with pain, allodynia, and dysesthesia after ITA harvest and can persist for up to 15 months. However, the true incidence and clinical impact of this entity has not been well charac-

Figure 5. Differences in total area of dysesthesia at discharge (pre-D/C), at 4 weeks, and at the 3-month follow-up in response to (A) light touch, (B) pinprick, and (C) temperature. D, Differences in the incidence of major sensory deficits (measuring at least 50 cm² in ≥2 sensory modalities) between skeletonized and nonskeletonized sides (*P<0.05; †P<0.001; ‡P=0.08).

Figure 6. Assessment tool used to map sensory deficits on the anterior chest wall. Representative sensory deficits from 1 patient are indicated (patient 19; response to pinprick sensation at the 4-week follow-up assessment).
terized. We found that patients did not discern any significant differences in postoperative pain between sides early after surgery. However, at the 3-month follow-up, skeletonization resulted in significantly reduced postoperative pain. The inability to identify differences early postoperatively may be due to competing sources of pain from the midline skin incision and sternotomy. At discharge, 16 patients (36%) reported reduced pain on the skeletonized side compared with the nonskeletonized side, whereas 13 (29%) reported the opposite; ie, there was a 7% absolute difference in the proportion of patients reporting discernible differences in pain, favoring skeletonization. This difference increased to 16% at 4 weeks and 23% at the 3-month follow-up, suggesting that ≈5 patients would need to receive a skeletonized ITA to reduce 1 occurrence of discernible pain at a 3-month follow-up.

Consistent with the finding of reduced pain, the areas of sensory deficits to light touch, pinprick, and temperature also were substantially reduced on the skeletonized side. These differences were present at discharge but further accentuated at follow-up because of improvements over time on the skeletonized side rather than worsening of deficits on the nonskeletonized side. The absolute risk difference in the incidence of major sensory deficits between skeletonized and nonskeletonized sides was 13% at discharge, 32% at 4 weeks, and 33% at 3 months. Thus, ≈3 patients would need to be treated with a skeletonized ITA to prevent the occurrence of 1 major sensory deficit at a 3-month follow-up. Overall, these findings support the idea that preservation of intercostal nerves through ITA skeletonization can reduce morbidity after ITA harvest.

This study was designed to evaluate early and side-specific effects of skeletonized versus nonskeletonized ITA harvest using a randomized, within-patient study design. As such, the benefits of skeletonization on sternal wound infection, which have been suggested in observational studies, could not be evaluated. Furthermore, long-term effects of skeletonization on graft flow, patency, and function were not assessed.

Although graft patency rates after skeletonized and nonskeletonized harvest have not been evaluated in randomized studies, several observational studies have reported early and midterm angiographic patency after ITA skeletonization. Excellent early patency rates (between 97% and 100%) have been reported by a number of groups in skeletonized left and right ITAs. Bical et al also have reported good skeletonized ITA patency (95.2%) at a midterm follow-up of 22 months. Calafiore et al compared patency rates between skeletonized and nonskeletonized ITAs in a subset of patients enrolled in an observational study and found similar patency between skeletonized and nonskeletonized ITAs both early (98.2% versus 97.5%) and at midterm follow-up (96.8% versus 94.3%; mean follow-up, 9.1 month). Although no studies have evaluated late angiographic patency, a number of studies have reported late clinical outcomes similar to that reported with nonskeletonized ITAs.

Conclusions

Skeletonized harvest of the ITA results in reduced pain and dysesthesia and in improved sternal perfusion. Skeletonization does not improve conduit flow but may increase conduit length. Skeletonization can reduce the morbidity associated with ITA harvest in patients undergoing CABG.

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Disclosures

None.

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**CLINICAL PERSPECTIVE**

The use of internal thoracic arteries (ITAs) for surgical coronary revascularization improves long-term outcomes. However, a number of limitations prevent routine use of these arteries as bypass conduits. These include limited conduit flow compared with vein grafts, limited conduit length, and the increased risk of sternal wound infections, particularly with bilateral ITA use, as a result of sternal hypoperfusion. Furthermore, ITA harvest has been associated with increased and persistent pain after surgery. Skeletonized harvest of the ITA, compared with the traditional nonskeletonized harvest, has been suggested to improve conduit flow, increase conduit length, and improve sternal perfusion. However, these benefits have been demonstrated only in observational studies. In this randomized, double-blind, within-patient comparison of skeletonized and nonskeletonized ITA harvest, ITA skeletonization did not lead to increased ITA flow and only demonstrated a trend toward an increase in length. There was significant improvement in sternal perfusion, postoperative pain, and sensory deficits with the skeletonized technique. Skeletonization did not result in increased ITA injury but required a slightly longer harvest time. This technique allows the harvest of an excellent conduit for bypass surgery while reducing morbidity.
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