Randomized Flow Capacity Comparison of Skeletonized and Pedicled Left Internal Mammary Artery

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Background. The preferential harvesting technique of the internal mammary artery has been periodically debated. This randomized study evaluated the flow outcome of the skeletonized versus pedicled left internal mammary artery.

Methods. Two hundred patients undergoing surgery for left anterior descending coronary artery revascularization were enrolled and randomized to pedicled (n = 100) or skeletonized (n = 100) harvesting. Intraoperative baseline flow and post adenosine infusion into the left ventricle, hospital outcome, echocardiographic results, and troponin I leakage were analyzed. Noninvasive periodic evaluation of flow was carried out at rest and during intravenous adenosine infusion by transthoracic Doppler ultrasound, and was stratified according to the harvesting technique. Final angiographic evaluation was performed by 64-slice multidetector computed tomography.

Results. Skeletonized left internal mammary arteries demonstrated better flow capacity at rest and during adenosine recruitment perioperatively and at all time points of follow-up. Troponin I leakage was significantly higher in the pedicled group (59 vs 42, $p = 0.02$). Pedicled harvesting (hazard ratio [HR] 3.6, 95% confidence interval [CI] 2.5 to 6.9, $p < 0.001$); indexed left ventricular mass greater than 150 g/m^2 (HR 4.6, 95% CI 3.1 to 7.5, $p < 0.001$); and baseline corrected thrombolysis in myocardial infarction frame count greater than 30 (HR 4.4, 95% CI, 3.8 to 7.2, $p < 0.001$) were the most powerful multivariable predictors of graft flow reserve less than 2.0. Postoperative echocardiographic results and clinical and angiographic outcomes were comparable between the two groups.

Conclusions. Skeletonization of the left internal mammary artery, beyond traditional proven advantages, provided significantly higher flow capacity and better graft flow reserve.

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The left internal mammary artery (LIMA) is the preferred conduit for coronary artery revascularization because of superior long-term patency rates and observational evidence of improved long-term outcomes [1, 2].

The preferential harvesting technique has been periodically debated. Skeletonization involves dissection of the LIMA away from the chest wall with preservation of collateral sternal blood supply. The LIMA skeletonization can provide some advantages, ranging from the achievement of a longer conduit with superior free flow [3–5] to decreased chest wall pain [6] and better pulmonary function [7]. The conduit skeletonization allows the preservation of the sternal blood supply with reduced incidence of wound complications [8] and, although technically more demanding, provides a graft with preserved integrity [9] and functionally active endothelium [10].

To date, besides traditional proven advantages, flow capacity in different LIMA harvesting techniques has been evaluated with contradictory results [4, 5]. Most current knowledge on this subject is supported primarily by observational studies that offer insufficient evidence for or against each harvesting technique. The randomized studies comparing the skeletonized to the pedicled LIMA are few and focused only on sternal perfusion [6, 11], vessel wall integrity [12], and vasoreactive profiles [10]. Major limitations of these randomized studies are the small sample sizes that may lead to unbalanced distribution of confounders, the limited relevance of the end points studied, the lack of postoperative LIMA flow evaluation, and angiographic assessment.

The present study was designed to evaluate early and medium term functional and angiographic results of skeletonized and pedicled LIMA harvesting in a randomized population of patients who underwent surgery for off-pump coronary artery by-pass grafting (CABG). The study aimed to test intraoperative free-flow capacity and flowmetric results before and during pharmacologic vasodilatation, and to investigate the coronary flow reserve by noninvasive determination serially over the first two year after surgery. Final angiographic evaluation of LIMA grafts was obtained by means of 64-slice multidetector computed tomography (CT).

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Material and Methods

Study Design and Patient Population

This was a prospective randomized study designed according to the Consolidated Standards of Reporting Trials statement and performed at the University Federico II in Naples. From May 2004 to June 2007, 200 patients under 80 years of age, undergoing primary off-pump coronary bypass surgery on a nonemergency basis, were enrolled. Contrast allergy, chronic atrial fibrillation, low ventricular function with an ejection fraction of less than 0.30, contraindications for off-pump surgery, additional cardiac or vascular surgical procedures, and severe systemic comorbidities (dialysis, hepatic failure, cancer, autoimmune disease) were exclusion criteria. Planned use of the LIMA for sequential grafting or for tangential anastomoses with the radial artery or right internal mammary artery were further exclusion criteria because the different hemodynamic rules underlying sequential and composite grafts might mislead flowmetric results. All patients underwent preoperative coronary angiography. Surgical indications were assessed as a 70% or greater diameter stenosis. Coronary stenoses were evaluated by the Quantitative Coronary Angiography Data System (Carddas Xi; Centricity GE Health Care Medical System, GE Healthcare, Burlington, VT). The number of coronary lesions was defined as the total number of stenosis 70% or greater in all coronary arteries. Coronary blood flow was assessed by means of the thrombolysis in myocardial infarction (TIMI) frame-counting method with a frame counter on the cine viewer. The longer left anterior descending (LAD) frame counts were corrected by dividing by 1.7 to derive the corrected TIMI frame count, as described by Gibson and colleagues [13]. According to study design, 100 patients were preoperatively randomized to receive a pedicled LIMA graft and 100 skeletonized a LIMA graft. The two groups were homogeneous, with minimal demographic and clinical differences (Table 1). Randomization was obtained by a computer-generated algorithm and was fully blinded, without any account of clinical or demographic features.

This study was approved by the Institutional Research Ethics Committee, and all patients provided written informed consent.

Table 1. Main Demographic and Clinical Characteristics in Skeletonized and Pedicled Groups

Characteristics	Pedicled (n = 100)	Skeletonized (n = 100)	p Value
Age	65 ± 12	67 ± 15	0.6
Gender (male)	68	71	0.7
BMI Kg/m^2	27.3 ± 4.5	28.8 ± 5.3	0.03
Diabetes	21	24	0.7
Hypertension	34	39	0.5
Dyslipidemia	41	44	0.7
HDL mg/dL	82 ± 21	79 ± 15	0.2
Creatinine mg/dL	0.7 ± 0.6	0.8 ± 0.7	0.3
Left main stem disease	15	13	0.8
Left ventricular hypertrophy (ILVM>125 mg/m^2)	22	24	0.8
Preoperative LVEF < 0.40	19	25	0.3
Left anterior descending CTFC	28.2 ± 9.3	26.5 ± 8.8	0.2

Values are mean ± SD or numbers.

BMI = body mass index; CTFC = corrected thrombolysis in myocardial infarction frame count; HDL = high density lipoprotein; ILVM = indexed left ventricular mass; LVEF = left ventricular ejection fraction.

Surgical Procedure

The pedicled LIMA was harvested together with veins and surrounding tissue. In the skeletonized group only the artery was mobilized and pulled down. The sternal and the anterior intercostal branches were occluded with hemoclips. Before clamping the distal part of the LIMA, the patients received 300 UI heparin/kg body weight intravenously to obtain an activated clotting time of longer than 400 seconds. Both pedicled and skeletonized LIMA were cut at the distal end 1 cm proximal to distal bifurcation. Two pedicled LIMA and two skeletonized LIMA, with unsatisfactory free flow after harvesting, were excluded from the study. Thereafter, 4 patients were enrolled and assigned to the two groups. All patients underwent off-pump CABG and the LIMA was always grafted on the LAD. Left-sided revascularization was obtained with the right internal mammary artery and the radial artery. Saphenous veins were usually used for right coronary artery revascularization. Mean graft for patients was 2.99 (1 to 5), the index of completeness was 0.99. Mean procedural time (time necessary to construct all distal anastomoses) was similar in both groups (p = 0.8). A suction-type mechanical stabilizer (Octopus; Medtronic Inc, Minneapolis, MN) was used to immobilize the target coronary artery; intracoronary shunts (Medtronic Inc) were routinely employed as well. Heart rate and blood pressure control were obtained pharmacologically and (or) with rotation of the operative table. Diltiazem (0.5 to 1.0 mg/kg) was infused intraoperatively and during the first 24 hours after surgery and was thereafter prescribed orally (100 to 200 mg/day). Ticlopidine was started 48 hours after the operation at a dose of 250 mg/day in both groups. Statin (rosuvastatin), started 24 hours before surgery at a dose of 20 mg/day, was administered over all follow-up time independent of cholesterol level.

Intraoperative Flow Measurement

Transit-time flowmeter (HT 323-CS; Transonic System Inc, Ithaca, NY) was employed for graft flow measurements.

Assessment of each LIMA was performed under stable hemodynamic conditions. Free flow was evaluated directly after distal division of the artery at zero resistance. Diluted papaverine (100 mg in 100 mL of lactate Ringer solution) was sprayed on the LIMA graft and the conduit was wrapped in a papaverine-soaked gauze and set aside until the second free flow was recorded just before the anastomosis. The final transit-time flowmeter measurement was obtained after all anastomoses had been completed and after 5 minutes of topically applied papaverine. The curves were coupled with the electrocardiographic tracing to correctly differentiate the systolic from the diastolic flow. The maximum, minimum, and mean flows were reported as mL/minute, and pulsatility index as an absolute number. Pulsatility index was defined as systolic peak flow minus diastolic bottom flow divided by the mean flow. The transit-time flowmeter measurements were interpreted as suggested by D'Ancona and colleagues [14].The graft flow reserve (GFR) was evaluated after hyperemic maximal flow induced with adenosine infused into the left ventricle through a needle at a concentration of 24 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Simultaneously, a standard lead of the echocardiogram and systolic, diastolic, and mean arterial pressures were recorded. The GFR was assessed as the ratio between hyperemic and baseline peak flow. All the baseline measurement were obtained with a mean arterial pressure at 80 mm Hg (mean 81 ± 11) and a heart rate between 70 and 85 pulse/minute (mean 78 ± 12).

Transthoracic Doppler Ultrasound and Graft Flow Reserve Evaluation

According to the previous demonstration that transthoracic Doppler echocardiography enabled an effective evaluation of LIMA graft function in over 90% of patients with high diagnostic power, we chose this totally noninvasive, and easily repeatable method for postoperative flow capacity assessment. The LIMA and LAD were imaged by a small multihertz transducer connected to an ultrasound system (GE VIVID 7; GE Healthcare). The LIMA flow velocities were measured by pulsed Doppler ultrasound under a color-coding guide. Systolic and diastolic peak and mean velocities were measured and three parameters were derived: diastolic-to-systolic peak velocity ratio, diastolic velocity time integral, and fraction diastolic velocity time integral divided by the diastolic plus the systolic velocity time integral. Doppler echocardiographic evaluation of graft flow velocity were measured at baseline and after maximal hyperemic response obtained within 90 seconds venous adenosine infusion (140 μg/kg/min). The GFR was the ratio between hyperemic and baseline peak diastolic flow velocities. For each test, three baseline and three hyperemic Doppler velocities were computed and averaged. Patients were evaluated seven days after surgery, at 3 months, and every 9 months thereafter. All substances that could interfere with the metabolism of adenosine, such as caffeine and other methylxanthine derivatives, were withheld 12 hours before the study; medication regimen was never changed. All patients were in sinus rhythm and a fasting state. Three patients in the pedicled group and one in the skeletonized group had contraindications to adenosine (heart block or reactive respiratory disease) and were considered ineligible for GFR evaluation. All patients had continuous electrocardiographic monitoring. Blood pressure was recorded at baseline, during adenosine infusion, and at recovery.

Angiographic Outcome

Radiographic angiography is considered the standard procedure for evaluation of coronary artery bypass grafts although it carries some risk of adverse events and cannot be used as follow-up in a large population of patients. Sixty- four-slice multidetector CT provides a noninvasive alternative allowing very good visualization of arterial conduits, especially of LIMA grafts [15]. All patients were scheduled for a 64-slice multidetector CT (Aquilion; Toshiba Medical Systems, Rome, Italy) angiographic evaluation of LIMA grafts 24 months after surgery.

Patients with a heart rate greater than 70 beats per minute before examination received 2 to 4 mg of intravenous propranolol 10 minutes prior to the scan. The three-dimensional images showed the lumen of each vessel. Two-dimensional reconstructions (curved multiplanar reformation) of the coronary arteries and grafts were performed on several planes to assess patency of grafts and anastomoses. Two experienced readers evaluated CT images by consensus reading. The quality of the anastomosis and conduit was graded according to Fitzgibbon and colleagues [16].

Perioperative Data

Echocardiographic evaluation was performed blindly to the assigned treatment preoperatively, 24 hours and 48 hours postoperatively, and at hospital discharge; left ventricular ejection fraction, wall motion score index, and indexed left ventricular mass were calculated. An indexed left ventricular mass of greater than 125 g/m^2 was considered a marker of left ventricular hypertrophy.

Troponin I was evaluated before surgery and at 8, 12, 24, and 48 hours after, and then on every postoperative day until hospital discharge. Upper normal limits were 0.5 ng/mL. Troponin I was assayed by means of a LIAISON kit (DiaSorin SpA, Saluggia, Italy).

Postoperative acute myocardial infarction was diagnosed when the three different criteria indicated by the Joint European Society of Cardiology/American College of Cardiology guidelines were fulfilled [17].

Statistical Analysis

The primary outcome for sample size calculation was LIMA flow before papaverine application. To detect an absolute difference of 5.2 mL/minute between skeletonized and nonskeletonized LIMA (20% increase in flow), with the assumption of a mean flow of 26.4 ± 16.1 mL/minute in the nonskeletonized group [5] at a 2-sided α level of 0.05 and 90% power, 85 pairs of LIMA were required. Allowing for a 10% to 12% dropout, we aimed to recruit 100 patients in each arm. Continuous variables were expressed as means ± standard deviation and categoric data as percentages. Comparisons of continuous variables between groups were performed with the Student *t* test for normally distributed features values. The Mann-Whitney *U* test was used for variables not normally distributed (transit-time flowmeter and GFR values) and categoric variables were analyzed with the χ^2

or Fisher exact tests when appropriate. Analysis of factors influencing graft flow and GFR values was performed calculating hazard ratio (HR) with 95% confidential intervals (CI). Multiway analysis of variance with correction for serial measurements was performed for Doppler ultrasound data evaluation. All variables with p values less than 0.05 were considered significant and were analyzed in a multivariate logistic regression model to assess the impact of each one on results. Statistical analysis was performed by SPSS version 13.0 for Windows (SPSS Inc, Chicago, IL).

Results

Early Postoperative Outcome

Patients with low output syndrome (1 from each group) were successfully treated with intraaortic balloon assistance. No significant differences were recorded between the two groups either in terms of recovery of left ventricle ejection fraction or wall motion score index. Troponin I leakage upper normal limit in both groups without any significant modification of left ventricle ejection fraction (50.2 ± 8.5 vs 49.2 ± 7.1, $p = 0.3$) and wall motion score index (1.2 ± 0.3 vs 1.2 ± 0.4, $p = 0.9$). No sternal wound infections were registered in the whole population of the study (Table 2).

Intraoperative Flow Evaluations

Free flow of the LIMA before application of papaverine was low in both groups (13.8 ± 13.0 mL/minute in the keletonized vs 18.8 ± 13.9 mL/minute in the pedicled, $p =$ 0.009). After treatment with papaverine the free flow had a significant increase in both groups (55.1 ± 24.5 in the pedicled group vs 63.8 ± 31.3 mL/minute in the skeletonized group, $p = 0.02$). Postanastomotic mean flows (30.31 ± 3.2 mL/minute vs 25.4 ± 11.1 mL/minute, $p =$ 0.0005) and pulsatility index (1.96 ± 0.7 vs 1.85 ± 0.8, $p =$ 0.04) were significantly better in the skeletonized group. During adenosine infusion, mean flows increased to 60.3 ± 5.6 mL/minute in the skeletonized group and to 48.8 ± 17.9 mL/minute in the pedicled group ($p = 0.0004$). The GFR value was 2.3 ± 1 in the skeletonized group versus 2.1 ± 0.8 in the pedicled group, $p = 0.1$. During the adenosine infusion mean arterial blood pressure decreased from 81 ± 11 to 75 ± 13 mm Hg ($p = 0.001$), and heart rate increased from 78 ± 12 to 92 ± 16 beats/minute ($p = 0.001$) (Table 3).

Significant univariate predictors of intraoperative GFR less than 2.0 were age greater than 65 years, diabetes, corrected TIMI frame count greater than 30, indexed left ventricular mass greater than 150 g/m^2, and pedicled harvesting. However, multivariate analysis of GFR less than 2.0 revealed that only corrected TIMI frame count greater than 30 (HR 4.4, 95% CI 3.8 to 7.2, $p < 0.001$), pedicled harvesting (HR 3.6, 95% CI 2.5 to 6.9, $p < 0.001$), and indexed left ventricular mass greater than 150 g/m^2 (HR 4.6, 95% CI 3.1 to 7.5, $p < 0.001$) were independent predictors of low GFR. Interestingly, multivariate analysis of GRF less than 2.0 revealed that indexed left ventricular mass greater than 150 g/m^2 was an independent predictor of low GFR in both groups (odds ratio 4.6, 95% CI 3.1 to 7.5, $p < 0.001$).

Transthoracic Doppler Ultrasound and Graft Flow Reserve Evaluation

Transthoracic Doppler Ultrasound follow-up was complete in 198 patients. Two patients (1 in the skeletonized group and 1 in the pedicled group) had LIMA flow indexes (diastolic-to-systolic peak velocity ratio < 1, diastolic velocity time integral fraction < 0.5, and GFR < 2) suggestive of a new LAD pathology confirmed by 64-slice multidetector CT and conventional angiography. One patient from the skeletonized group had a myocardial infarction nine months after surgery for occlusion of a radial artery and was not further evaluated for GFR; two patients from the pedicled group were lost, respectively, 12 and 21 months after surgery.

In 191 patients (98%) detection of the LIMA was successful. Intraluminal flow signals showed a biphasic flow pattern with a prevalent diastolic component. All patients were in sinus rhythm. Neither the heart rate nor the systolic or diastolic blood pressure was significantly different between the groups before and during hyperemic response. Maximal increase in coronary flow velocity was obtained within 60 seconds of drug infusion and flow returned to baseline within 30 seconds of discontinuing the drug. No major adverse reactions occurred during or after adenosine infusion. Diastolic peak velocity, diastolic-to-systolic peak velocity ratio, and diastolic velocity time integral fraction increased from baseline in both groups. Nevertheless, skeletonized conduits confirmed statistically better early and medium term results as compared with pedicled grafts, both in terms of

Table 2. Early Postoperative Outcome

	Pedicled (n = 100)	Skeletonized (n = 100)	p Value
Hospital death	1	—	0.5
Number of anastomosis/patient	3.1 ± 1.2	2.9 ± 1.5	0.2
Completeness index	0.98	0.99	0.9
Ventilation time (hours)	5.2 ± 3.1	5.3 ± 4.1	0.8
Intensive care unit stay (days)	2.5 ± 1.4	2.3 ± 2.1	0.4
Hospital stay (days)	7.4 ± 2.3	7.8 ± 2.1	0.2
Chest tube draining in 24 hours (mL)	320 ± 150	370 ± 160	0.02
Revision for bleeding	1	2	0.5
PAMI	3	2	0.5
Troponin I > 0.5 ng/mL	59	42	0.02
Mean troponin I peak values (ng/mL)	0.58 ± 0.31	0.49 ± 0.25	0.02
Low output syndrome	1	1	0.8
Transient renal failure	1	—	0.5
Inotropic support	35	31	0.6
Sternal wound infection	0	0	—

Values are mean ± SD or numbers.

PAMI = perioperative acute myocardial infarction.

Table 3. Transient Time Flow Results in Pedicled Versus Skeletonized Left Internal Mammary Artery Graft

	Pedicled (n = 100)	Skeletonized (n= 100)	*p* Value
Free flow (mL/minute):			
Before papaverine	18.8 ± 13.9	13.8 ± 13.1	0.009
After papaverine	55.1 ± 24.5	63.8 ± 31.3	0.02
After anastomosis:			
Maximum flow	49.2 ± 13.2	55.3 ± 15.3	0.002
Mean flow	25.4 ± 11.1	30.3 ± 13.2	0.0005
Minimum flow	2.9 ± 1.1	2.3 ± 0.8	0.007
PI	1.96 ± 0.7	1.85 ± 0.8	0.04
After adenosine:			
Mean flow	48.8 ± 17.9	60.3 ± 15.6	0.0004
PI	2.4 ± 0.8	2.1 ± 1.1	0.02
GFR	2.1 ± 0.8	2.3 ± 1.0	0.1

Values are mean ± SD.
GFR = graft flow reserve; PI = pulsatility index.

velocity indexes and GFR at all time points of follow-up (Table 4).

Sixty-Four-Slice Multidetector Computed Tomography

The multidetector CT was completed in 195 patients. Mean heart rate during data acquisition was 55.8 ± 4 beats/minute. A total of 195 LIMA conduits were available for the analysis. Problems for artifacts from metal clips alongside LIMA grafts were registered in 3 patients. Excellent graft visualization including anastomoses was achieved in all the other scanned grafts of both groups. Significant stenoses have not been evidenced in either of the two groups.

Comment

We report within-patient randomized comparison of skeletonized and pedicled LIMA harvest, focusing on flow evaluation at rest and after hyperemic maximal flow, assessed intraoperatively and serially over two years of follow-up. The strict enrollment criteria, focused to obtain two very homogeneous randomized study arms, eliminated the confounding effect of numerous patient variables that could potentially influence conduit flow. Contrary to the results of previously published studies [6, 18], but in large agreement with others [3–5], we found that skeletonization provides significantly higher LIMA flow capacity either in terms of flow values, flow curve patterns, and PI, or in terms of GFR when hyperemic maximal flow was induced. The differences between the two groups tend to disappear over time. In fact, resting flow in the pedicled LIMA group gradually rises from 7 days to 21 months suggesting that the behavior of pedi-

Table 4. Doppler Ultrasound Data in Skeletonized and Pedicled Groups at Baseline and After Adenosine Infusion

	Group	7 Days	3 Months	12 Months	21 Months	Between Group	Within Group	Interaction
Baseline:								
DPV (m/second)	P	0.24 ± 0.12	0.29 ± 0.12	0.35 ± 0.9	0.40 ± 0.07	0.03	0.001	0.01
	S	0.3 ± 0.11	0.34 ± 0.14	0.38 ± 0.11	0.42 ± 0.04		0.003	
SPV (m/second)	P	0.16 ± 0.08	0.17 ± 0.08	0.17 ± 0.1	0.17 ± 0.01	0.02	0.06	0.03
	S	0.19 ± 0.1	0.21 ± 0.09	0.18 ± 0.08	0.18 ± 0.05		0.05	
DSPV	P	1.49 ± 0.28	1.47 ± 0.2	1.71 ± 0.19	2.12 ± 0.2	0.04	0.03	0.03
	S	1.58 ± 0.21	1.56 ± 0.28	1.8 ± 0.31	2.2 ± 0.23		0.02	
DVTI (m)	P	0.08 ± 0.04	0.09 ± 0.01	0.1 ± 0.02	0.12 ± 0.07	0.07	0.02	0.05
	S	0.1 ± 0.05	0.1 ± 0.04	0.12 ± 0.05	0.14 ± 0.06		0.06	
DVTI/DVTI+SVI	P	0.65 ± 0.2	0.65 ± 0.3	0.71 ± 0.28	0.84 ± 0.21	0.03	0.02	0.04
	S	0.72 ± 0.1	0.72 ± 0.2	0.83 ± 0.23	0.88 ± 0.19		0.04	
Adenosine:								
DPV (m/second)	P	0.52 ± 0.12	0.56 ± 0.15	0.77 ± 0.15	0.78 ± 0.13	0.03	0.03	0.03
	S	0.60 ± 0.24	0.63 ± 0.26	0.82 ± 0.12	0.82 ± 0.11		0.01	
SPV (m/second)	P	0.24 ± 0.08	0.24 ± 0.10	0.24 ± 0.81	0.24 ± 0.09	0.04	0.07	0.05
	S	0.27 ± 0.10	0.28 ± 0.11	0.27 ± 0.11	0.27 ± 0.51		0.06	
DSPV	P	2.0 ± 0.40	2.10 ± 0.20	2.95 ± 0.32	3.12 ± 0.32	0.02	0.01	0.04
	S	2.20 ± 0.71	2.25 ± 0.4	3.0 ± 0.54	3.02 ± 0.41		0.04	
DVTI (m)	P	0.18 ± 0.06	0.19 ± 0.81	0.21 ± 0.74	0.25 ± 0.06	0.06	0.04	0.04
	S	0.20 ± 0.04	0.21 ± 0.62	0.24 ± 0.92	0.29 ± 0.09		0.02	
DVTI/DVTI+SVI	P	0.68 ± 0.09	0.68 ± 0.12	0.74 ± 0.13	0.86 ± 0.14	0.07	0.03	0.06
	S	0.72 ± 0.11	0.73 ± 0.12	0.81 ± 0.17	0.91 ± 0.16		0.02	
GFR	P	2.14 ± 0.14	2.16 ± 0.16	2.18 ± 0.4	2.21 ± 0.3	0.03	0.04	0.04
	S	2.18 ± 0.1	2.2 ± 0.11	2.28 ± 0.3	2.29 ± 0.2		0.03	

DPV = diastolic peak velocities; DSPV = diastolic-to-systolic peak velocity ratio; DVTI = diastolic velocity time integral; DVTI/DVTI + SVI = diastolic fraction of velocity-time integral; GFR = graft flow reserve: adenosine infusion to baseline ratio of peak diastolic velocities; P = pedicled; S = skeletonized; SPV = systolic peak velocities; SVI = stroke volume index.

cled LIMA grafts increases gradually over the follow-up time, probably due to an adaptive effect with a prevalent late vasodilatory response [4]. Additionally, and interestingly, our results evidenced that coronary flow during pharmacologic recruitment and coronary flow reserve remained significantly higher at any point of follow-up in patients from the skeletonized group. These results are of difficult interpretation and were neither followed by any superior midterm clinical benefits nor by advantages in morbidity and cardiac function. However, it should be considered that our population study was strictly selected, had a low surgical risk, and underwent uncomplicated surgical procedures.

In our opinion, skeletonized harvesting leads to improved coronary flow reserve and could involve a number of potential positive clinical implications. Left internal mammary artery flow, challenged by increased myocardial demand, may not be sufficient to meet the metabolic demands of the myocardial segments it subtends in critical cases.

The mechanism by which skeletonization might improve flow has not been ascertained. It has been reported that skeletonization increases graft diameter and, therefore, decreases resistance [5]. Presumably, the skeletonization facilitates the vasodilating action of papaverine because topical papaverine may reach more of the naked skeletonized internal mammary than when it is hidden in a pedicle. Nonetheless, other and more complex histologic and functional issues need a definitive assessment to better define early and late postoperative behavior of LIMA conduits.

Interestingly, the results from multivariate logistic regression analysis of GFR less than 2.0 in the whole population of study revealed that low GFR was strictly linked to corrected TIMI frame count greater than 30, indexed left ventricular mass greater than 150 g/m^2, and pedicled harvesting. Consequently, in patients with poor LAD run-off and left ventricular hypertrophy the use of a skeletonized LIMA graft could be mostly indicated.

A further finding of our study was the evidence of a slight, but statistically significant, higher troponin I values in patients from the pedicled group despite similar procedural time. The meaning of troponin I increase, particularly those after uncomplicated surgical procedures, remains a controversial issue. Nevertheless, it is largely accepted that troponin I leakage is the best sensitive and specific marker of myocardial damage. It can occur in low perfusion states and is a predictor of early and late adverse clinical events [19]. Hence, we feel that an absolute reduction of marker release, as provided by skeletonized LIMA, would translate into a reduction of early and late adverse events.

Despite better flow capacity and GFR of skeletonized grafts, the echocardiographic findings, blood transfusion need, ventilation times, and intensive care unit and hospital stays were comparable between both groups.

This study provides a complete angiographic evaluation of all patients; skeletonized and pedicled LIMA showed similar conduit quality and patency rates two years after surgery. However, our follow-up was not long enough to provide exhaustive results on such topics that should be assessed over ten years after surgery and the variable graft patency, which occurs at very low rates, needs a very large sample for statistical strength. Nonetheless, our results provide evidence that early graft patency appears to be unaffected by the harvesting technique.

Finally, the study was designed for a randomized comparison between pedicled and skeletonized LIMA harvesting methods in patients who underwent off-pump CABG with LIMA to LAD. Therefore, we have no data to acknowledge that our results may apply to on-pump CABG as well. In conclusion, our findings in addition to the evidence that LIMA skeletonization does not affect the conduit patency and the traditional proven advantages of skeletonized LIMA could currently justify the expanded use of skeletonized LIMA as a conduit of choice for myocardial revascularization.

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INVITED COMMENTARY

The present success of surgical coronary artery revascularization is predominantly based on the superior patency of the internal thoracic artery (ITA) graft. There is growing evidence that the use of bilateral ITA grafts results in a significant decrease of subsequent cardiac events such as recurrent ischemia and need for repeat revascularization. However, the most important objection for bilateral ITA grafting is related to the increased risk of sternal wound healing problems, particularly in diabetic patients.

Skeletonization of the ITA has been advanced as a technical modification to reduce this complication by better preservation of sternal blood supply. Moreover, it offers the supplementary advantage of increased graft length, beneficial for maximal arterial coronary artery revascularization. Most surgeons still prefer to harvest the ITA graft as a pedicle to prevent graft spasm and iatrogenic damage. Meanwhile, protagonists of the skeletonization technique have made a lot of efforts to demonstrate the preservation of vascular integrity of the ITA by respecting a careful and diligent dissection technique.

The clinical performance of skeletonized conduits is mainly assessed by retrospective or small-sample randomized trials focusing on different points of interest with an often low occurrence rate. In this study, Mannacio and colleagues [1] looked specifically to the flow capacity of the ITA in a randomized comparison between both harvesting techniques. Measurement of early free and postanastomotic flow at baseline and after adenosine administration favored the skeletonized graft. A similar approach using transthoracic Doppler ultrasound imaging also showed an advantage flow pattern for skeletonization at 21 months of follow-up, with slight attenuation of the perioperative differences. However, there was no difference in early patency by multislice computed tomography angiographic control.

The authors should be congratulated for this strict and well-designed study, which can serve as a reference work in the ongoing debate concerning the optimal method of ITA harvesting. Besides the proven benefit of skeletonization on sternal wound healing, the direct clinical effect of superior flow capacity of the ITA graft remains discussable. Although one might intuitively argue that improved flow equals improved patency, there is little scientific evidence of this relationship. Therefore, I would like to agree with the authors to suggest that longer-term studies are needed, showing at least a concurrent patency rate of skeletonized ITA vs the currently established pedicled ITA, to raise this issue above the controversy between belief and evidence before changing widely a surgeon's common practice.

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