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Evaluation of Flow in the Left Anterior Descending Coronary Artery But Not in the Left Internal Mammary Artery Graft Predicts Significant Stenosis of the Arterial Conduit

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OBJECTIVES The purpose of this study was to evaluate which Doppler-derived flow index best predicts new distal left anterior descending coronary artery (LAD) stenosis in patients with left internal mammary artery (LIMA) graft.

BACKGROUND The LIMA flow measurement has been proposed to assess graft function, but it may be misleading in case of new distal LAD stenosis and/or competitive flow from native LAD. Distal LAD coronary flow reserve (CFR: hyperemic/baseline peak flow velocity ratio) may be more appropriate.

METHODS The LIMA and distal LAD flow was measured by transthoracic Doppler echocardiography in 96 patients undergoing diagnostic/therapeutic coronary angiography, 7 ± 4 years after cardiac bypass surgery. The LIMA flow indexes (systolic-to-diastolic peak velocity ratio [SDPVr] >1, diastolic time velocity integral fraction [DTVIf] <0.5, and CFR <2) and LAD CFR <2 were used to predict ≥70% new LAD stenosis.

RESULTS The LAD CFR <2 predicted new LAD stenosis, found in 21 of 77 patients without competitive flow from native LAD, with significantly higher diagnostic accuracy (98%) than LIMA flow indexes (SDPVr >1 = 61%, DTVIf <0.5 = 69%, and CFR <2 = 72%). The LIMA flow indexes were abnormal in 17 of 19 patients with competitive graft flow, but only 5 had graft restriction, and none had significant LAD stenosis. In a multivariate model of new distal LAD stenosis prediction, competitive flow from native LAD reduced the predictive role of LIMA but not of LAD CFR.

CONCLUSIONS In patients without competitive flow from native LAD, LAD CFR is more accurate for the detection of LAD stenosis than LIMA CFR. In patients with competitive graft flow, abnormal LIMA flow patterns and blunted LIMA CFR do not reflect downstream LAD flow as LAD CFR does. (J Am Coll Cardiol 2005;45:424–32) © 2005 by the American College of Cardiology Foundation

Myocardial revascularization with the left internal mammary artery (LIMA) over the left anterior descending coronary artery (LAD) is the most used surgical strategy in patients with coronary artery disease, owing to an excellent long-term patency profile (1).

Transthoracic Doppler ultrasound has been proposed to study the LIMA-LAD conduit (2–8). In the early 1990s, the available technology allowed one to measure flow in the LIMA only from a mid-left parasternal (2) or a supraclavicular approach (3–5,7,8), at its take-off from the left subclavian artery, but not in the distal LAD. Either resting flow or coronary flow velocity reserve (CFR) in the LIMA were used to assess graft function. However, sampling the graft may be misleading, because: 1) graft flow may not predict a new distal LAD stenosis, because proximal to the stenosis the flow may be preserved (9); and 2) competitive flow from the native LAD may impair mammary flow and blunt mammary flow reserve, even in the absence of any graft stenosis. Recent advances in transthoracic color-Doppler ultrasound technology allowed imaging of the distal LAD (10,11) for the noninvasive detection of recanalization in acute anterior myocardial infarction (12), diagnosis of LAD disease by measurement of CFR (13,14), monitoring of changes in CFR after stenting (15,16), and the study of microcirculation in coronary artery disease (17).

Sampling the distal LAD in patients with LIMA graft may overcome the aforementioned limitation of sampling only the LIMA. We have therefore compared several flow-derived indexes of the LIMA graft and distal LAD to find which parameter best predicts the function of the LIMA-LAD conduit, with particular regard to a new distal LAD stenosis.

METHODS

Study patients. One hundred consecutive patients with LIMA-LAD graft, referred for coronary angiography, were

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Abbreviations and Acronyms

CFR = coronary flow velocity reserve
DVTI = diastolic velocity time integral
LAD = left anterior descending coronary artery
LIMA = left internal mammary artery
SDPV = systolic-to-diastolic peak velocity

evaluated with transthoracic Doppler echocardiography for noninvasive assessment of LIMA-LAD conduit function. Ninety-six patients (82 males, 14 females, age 62 ± 8 years, range 35 to 77 years), 15 with isolated LIMA graft and 81 with associated saphenous vein grafts, had adequate assessment of CFR in the LIMA and distal LAD. One patient had a normally functioning prosthetic aortic valve. Transthoracic Doppler echocardiography was performed 7 ± 4 years (range 0.8 to 18 years) after successful cardiac surgery and 24 to 48 h before coronary angiography. Exclusion criteria were: acute coronary syndrome, previous myocardial infarction, left ventricular hypertrophy, congestive heart failure, significant valvular heart disease, and contraindications to adenosine administration. All patients were in sinus rhythm and fasting state, and provided written informed consent. All coronary active medications were withdrawn the day before the Doppler study.

Transthoracic Doppler ultrasound. The LIMA and LAD were imaged as previously described (2,6,10,15–17), in the left lateral decubitus, by a small multi-hertz transducer connected to an ultrasound system (Sequoia C256; Siemens-Acuson, Mountain View, California), allowing independent change of frequency between two-dimensional (3.5 to 7.0 MHz) and color Doppler ultrasound (3.5 to 6.0 MHz). The LIMA and LAD flow velocities were measured by pulsed Doppler ultrasound under color-coding guide. Briefly, to image the LIMA, the left parasternal area between the second and fourth intercostal space was scanned. The LIMA graft was identified as a tubular structure with color flow directed from base to apex, and blood flow velocity was recorded by pulsed Doppler ultrasound. The distal LAD was imaged from the fourth to fifth left intercostal space in the interventricular groove, using a modified two-chamber view (13). Care was taken to visualize the most distal tract of the artery in the periapical area. The best long-axis view in color Doppler flow imaging was obtained to maintain a $<30^{\circ}$ angle between flow and Doppler ultrasound beam. The LAD flow velocity was measured by pulsed Doppler ultrasound. All studies were continuously recorded on a half-inch S-VHS videotape, and still-frames were digitally acquired and stored in a magneto-optical disk for off-line analysis. Systolic and diastolic peak and mean velocities were measured in the LIMA and LAD, and two resting LIMA flow parameters were derived (2): systolic-to-diastolic peak velocity (SDPV) ratio, and diastolic velocity time integral (DVTI) fraction (DVTI divided by the diastolic plus the systolic velocity time integral). The CFR was measured in the LIMA and distal LAD by 90-s venous adenosine infusion (140 mcg/kg/min) as the ratio between hyperemic and baseline peak flow velocities. For each test, three baseline and three hyperemic Doppler velocities were computed and averaged. All patients had continuous heart rate and electrocardiographic monitoring. Blood pressure was recorded at baseline, during adenosine infusion, and at recovery, for each test. An SDPV ratio >1 in the LIMA (2), DVTI fraction <0.5 in the LIMA (2), and CFR <2 in the LIMA and distal LAD were used to predict significant ($\geq$70%) stenosis along the graft-to-LAD conduit (13,16,18,19). Flow parameters were measured blind to clinical and angiographic results.

Coronary angiography. Cardiac catheterization was performed by the percutaneous femoral approach. The LIMA, aortocoronary grafts, and native coronary arteries were selectively visualized. Vessel lumen diameters were measured online by electronic calipers, by two expert operators, blind to the Doppler results. The outer diameter of the fluid-filled diagnostic/therapeutic catheter, centered, was used as a scaling device to obtain absolute arterial dimensions. Two orthogonal projections of the graft and/or the coronary artery lesion at end-diastole were used to measure percent lumen narrowing, if present. A graft and/or distal LAD stenosis $\geq$70% was considered significant.

Reproducibility of coronary flow reserve. Inter- and intraobserver variability of coronary Doppler ultrasound measurements in our laboratory are 3.2% and 2%, respectively (13), whereas intra-individual variability never exceeds 2 cm/s, providing a maximal ±6% difference in relative terms (15).

Statistical analysis. Data are expressed as mean ± SD. The BMDP software (University of California Press, Berkeley, California, 1990) was used. When data expressed proportions, average values were used in most cases. Intergroup differences were assessed by *t* tests with separate variance (BMDP-7D). Sensitivity, specificity and diagnostic accuracy were calculated and compared using chi-square results (BMDP-4F). Cutoff values were determined selecting points of potential clinical value based on literature data, namely <2 versus ≥ 2 for CFRs (13,16,18,19), >1 versus ≤ 1 for SDPV ratio (2), and <0.5 versus ≥ 0.5 for DVTI fraction (2). Chi-square test was also used to test significance for proportions. All possible subsets analysis (BMDP-9R) was used to predict multivariately (20), by using a linear model, the presence of new distal LAD stenosis. A series of 10 basal covariates was considered, and four different models were run to compare the role of either CFR in the LAD or LIMA and the respective contribution of LIMA flow type in the presence of either CFR in the LAD or LIMA as independent covariates. F-statistics and standard parameters produced by BMDP-9R were used to compare the four models. A comprehensive evaluation of all these parameters enabled conclusions about significance of differences. A p value <0.05 was considered statistically significant.

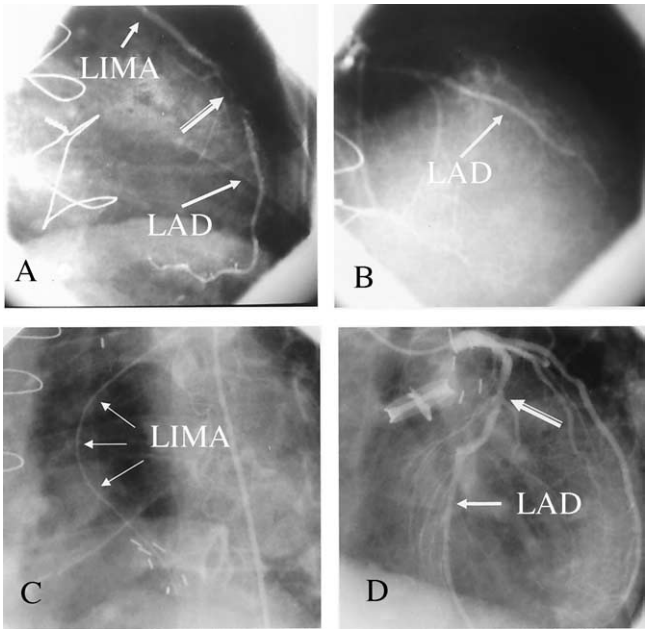

Figure 1. Selective coronary angiography of the left internal mammary artery (LIMA) and the left anterior descending coronary artery (LAD). **(Upper panels)** Competitive flow without graft restriction. **(A)** Injection in the LIMA. The **empty arrow** points to the joining tract, where flow entering from the LIMA is stopped by non-contrasted blood coming from the proximal LAD. **(B)** Injection in the left main shows anterograde filling of the LAD. **(Lower panels)** Competitive flow with graft restriction. **(C)** The dye selectively injected into the LIMA partially fills the graft, which is thin **(arrows)** and does not allow the contrast to reach the joining tract. **(D)** Contrast injection in the left main shows anterograde filling of the LAD, with 30% middle tract stenosis **(empty arrow).**

RESULTS

Coronary angiography. Seventy-seven patients had proximal occlusion of the LAD that was distally supplied only by the graft (non-competitive LIMA flow from the native LAD, Group A). Nineteen patients had an open proximal LAD with competitive flow between the graft and the native LAD (Group B): in 14 of 19 patients the graft was patent, and injection of dye in the graft or in the LAD alternatively produced at the joining tract (watershed area) a wash-in and washout effect (Figs. 1A and 1B); in 5 of 19 patients the distal LIMA was diffusely restricted (≥70% stenosis) (Figs. 1C and D) (21). In Group A, 21 patients (27.3%) had a significant (≥70%) new stenosis of the LAD after the anastomosis, whereas in Group B, none of 19 patients had significant LAD narrowing (percent diameter stenosis 40 ± 14%, range 20% to 60%).

None of the patients had collateral vessels from the LAD to other coronary arteries and vice versa.

Transthoracic Doppler ultrasound. Groups were not statistically different regarding risk factors, demographic and clinical variables, but had different Doppler-derived flow dynamics (Table 1). Baseline LIMA flow was predominantly diastolic in Group A (Fig. 2A), whereas it was balanced (n = 6) or predominantly systolic (n = 13) in Group B (Figs. 2E and 2G). These flow patterns produced significantly higher SDPV ratio and lower DVTI fraction in Group B than in Group A (Table 1), indicating restricted graft flow in Group B.

Table 1. Study Population

	Group A: Non-Competitive LIMA Flow (n = 77)	Group B: Competitive LIMA Flow (n = 19)	T (Separate Variance)	p Value
Demographic variables				
Gender (male/female = 1/0)	0.896	0.789	1.04	NS
Age (yrs)	62 ± 9	63 ± 7	−0.36	NS
Body surface area (m^2)	1.86 ± 0.12	1.88 ± 0.18	−0.31	NS
Clinical variables				
LVEDP (mm Hg)	13 ± 3	13 ± 4	0.19	NS
Left ventricular ejection fraction (%)	56 ± 6	56 ± 5	0.08	NS
Left ventricular wall motion score index	1.15 ± 0.21	1.20 ± 0.26	−0.83	NS
Left ventricular hypertrophy (yes/no = 1/0)	0.351	0.421	−0.55	NS
Previous acute myocardial infarction (yes/no = 1/0)	0.325	0.368	−0.35	NS
Distal LAD stenosis ≥70% (%)	27.3	0	6.63†	<0.01
LIMA stenosis ≥70% (%)	0	26.3	21.38†	<0.0001
Risk factors (yes/no = 1/0)				
Cholesterol	0.766	0.632	1.09	NS
Diabetes mellitus	0.156	0.211	−0.52	NS
Hypertension	0.494	0.526	−0.25	NS
Smoker	0.610	0.684	−0.60	NS
Doppler ultrasound flow-derived variables				
SDPV LIMA ratio	0.81 ± 0.32	1.68 ± 0.81	−4.57	<0.001
DVTI LIMA fraction	0.70 ± 0.08	0.55 ± 0.12	5.05	<0.0001
CFR LIMA (peak velocity)	2.45 ± 0.86	1.40 ± 0.34	8.40	<0.0001
CFR LAD (peak velocity)	2.45 ± 0.99	2.95 ± 0.38*	−3.50	<0.001
Absolute difference between LIMA and LAD peak CFR	0.004 ± 0.73	−1.55 ± 0.47	11.36	<0.0001

*The higher CFR in the LAD in patients with flow competition reflects the absence of significant (≥70%) distal LAD stenosis in this group, conversely 21 patients without competitive flow had significant LAD stenosis. †These values are chi-square. Data are mean ± SD (also for variables having % values); only mean for variables representing proportions.

CFR = coronary flow reserve; DVTI = diastolic velocity time integral; LAD = left anterior descending coronary artery; LIMA = left internal mammary artery; LVEDP = left ventricular end-diastolic pressure; SDPV = systolic/diastolic peak velocity.

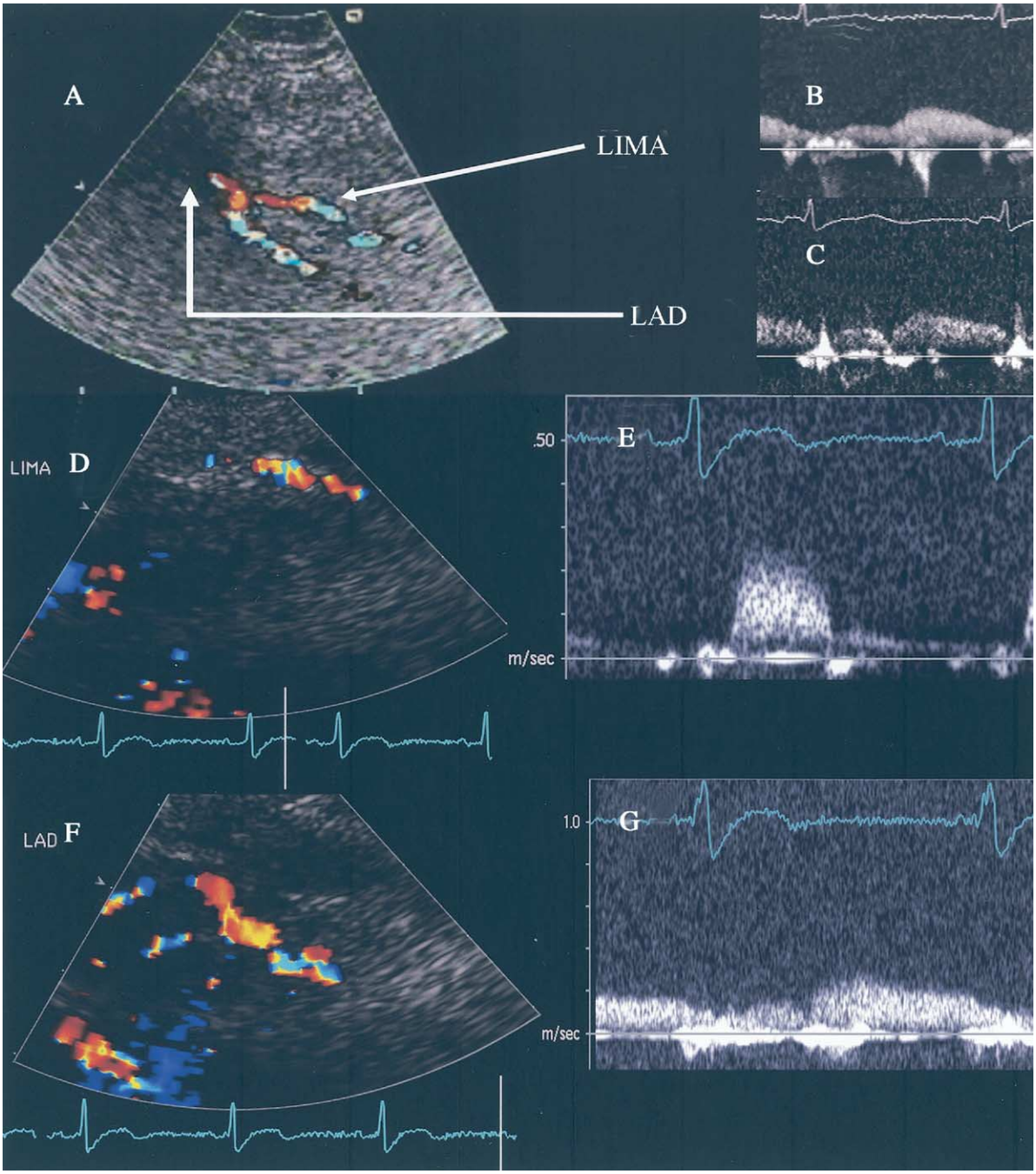

Figure 2. Resting transthoracic color-Doppler ultrasound. **(A to C)** Patient without competitive left internal mammary artery (LIMA) graft flow. Color Doppler **(A)** shows LIMA and left anterior descending (LAD) flows **(arrows),** and corresponding pulsed Doppler ultrasound shows prominent diastolic velocity **(B and C). (D to G)** Patient with flow competition. The LIMA flow **(D and E)** shows a prominent systolic and a very low diastolic component, whereas LAD flow **(F and G)** is mainly diastolic.

In Group A, CFR was superposable in the LIMA and LAD (absolute difference 0.004 ± 0.73) (Table 1, Fig. 3). In 21 patients with significant distal LAD stenosis, CFR in the LIMA overestimated that in the LAD (1.64 ± 0.77 and 1.27 ± 0.30, respectively), being in 5 patients even >2 (Fig. 4). In Group B, CFR in the LIMA was lower than that in the LAD (absolute difference −1.55 ± 0.47) (Table 1, Fig. 5), but it could not predict whether the graft was restricted (n = 5, CFR = 1.46 ± 0.34) or full patent (n = 14, CFR = 1.23 ± 0.32). Of note, LIMA flow indexes were abnormal (higher SDPV ratio, lower DVTI fraction, and blunted CFR) in 17 of 19 patients with competitive graft flow, but only 5 had graft restriction, and none had significant LAD stenosis.

The univariate analysis showed that CFR in the LAD had a higher diagnostic accuracy to predict a significant new distal LAD stenosis compared with the other Doppler ultrasound parameters measured in the LIMA (Table 2).

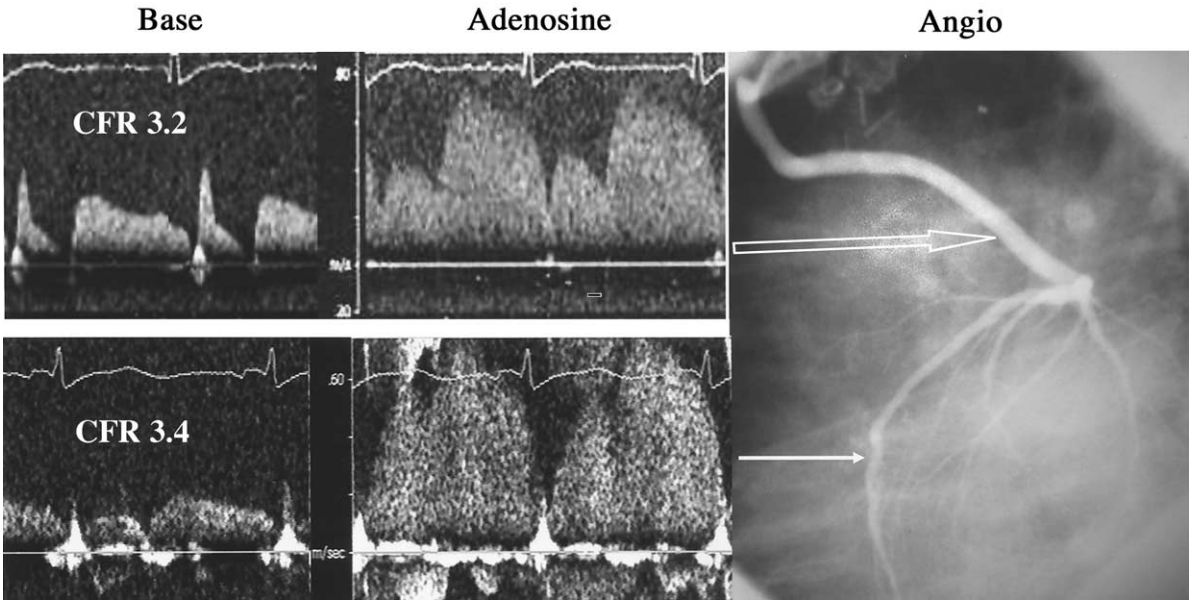

Figure 3. Patient with occluded proximal left anterior coronary artery (LAD), without competitive left internal mammary artery (LIMA) flow. The flow velocity reserve (CFR) was similar when assessed either at the level of the LIMA **(empty arrow),** or at the level of the LAD **(white arrow).**

Conversely, the Doppler-derived LIMA flow indexes (SDPV ratio >1, DVTI fraction <0.5, and CFR <2) had a low diagnostic accuracy in predicting graft restriction (Table 2). Finally, sensitivity, specificity, and diagnostic accuracy of LIMA CFR to predict LAD CFR were respectively 42.5%, 89.3%, and 69.8% (chi-square 12.94, $p < 0.0003$), which is in overall agreement with the results shown in Table 2, where LIMA and LAD CFR are assessed with regard to the respective predictive role of either LIMA or LAD stenoses.

The multivariate analysis showed that the best predictor of significant new LAD stenosis was CFR in the LAD (Table 3, model A). Moreover, CFR in the LIMA contributed less than one-third of CFR in the LAD to the prediction of distal LAD stenosis (Table 3, model B). Flow competition from the native LAD was the main confound-

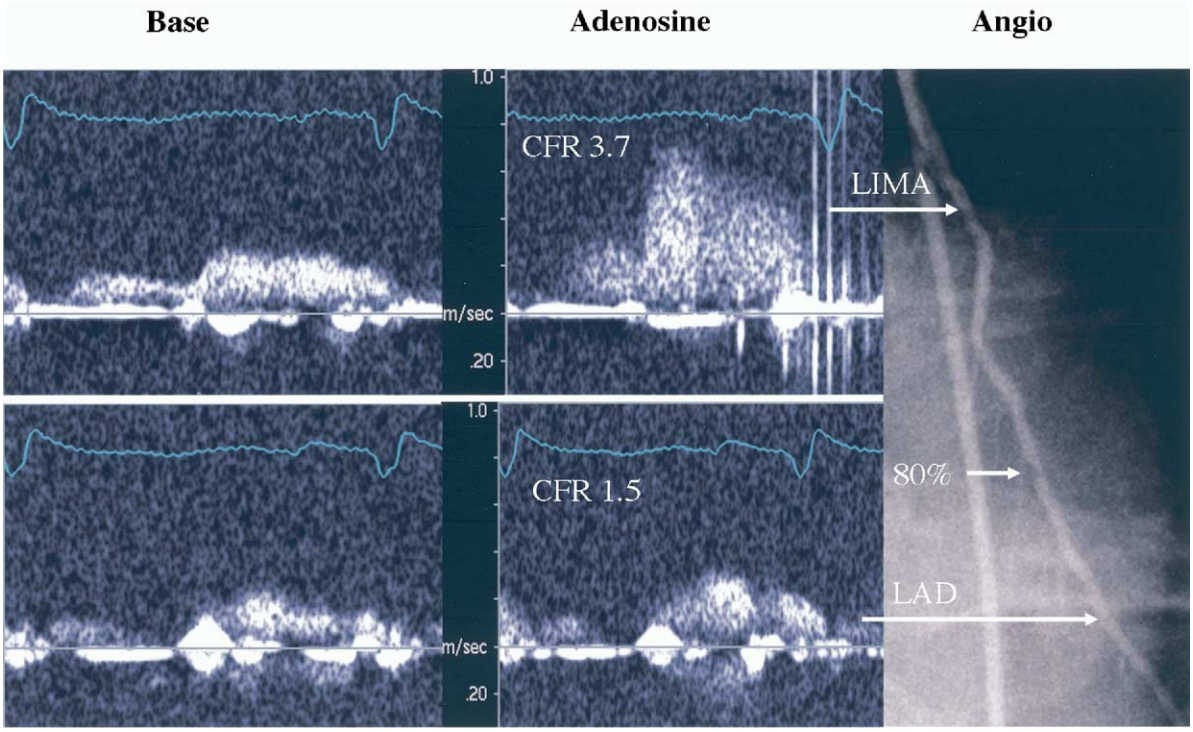

Figure 4. Patient without competitive left internal mammary artery (LIMA) flow, occluded proximal left anterior descending coronary artery (LAD), and 80% distal, post-anastomotic LAD stenosis. The coronary flow reserve (CFR) in the LIMA is 3.7, whereas in the distal LAD it is 1.5.

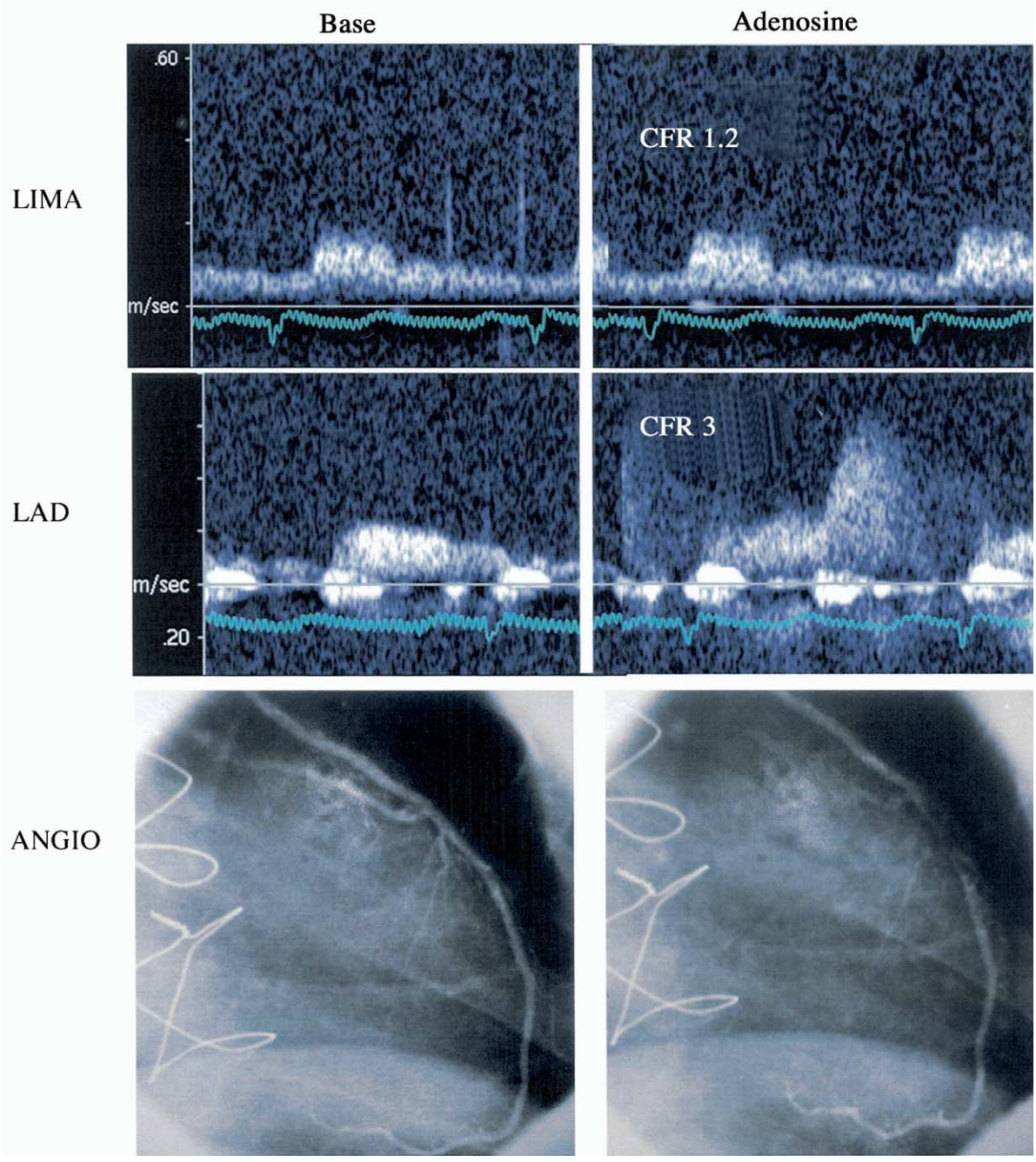

Figure 5. Patient with flow competition. **(Upper panels)** Flow velocity in the left internal mammary artery (LIMA) shows a higher systolic than diastolic component and a markedly abnormal coronary flow velocity reserve (CFR). **(Middle panels)** CFR, measured in the distal left anterior descending coronary artery (LAD), was normal. **(Lower panels)** Coronary angiography showed that the LIMA was proximally patent, but contrast material stopped at the joining tract. There was no flow limiting stenosis in the distal LAD after the anastomosis.

ing factor when LIMA flow parameters were used to predict distal LAD stenosis (Table 3, models C and D). Globally (Table 3), when CFR was measured in the LAD (with or without LIMA flow type consideration, i.e., presence or absence of competitive graft flow), prediction of distal LAD stenosis was good (taking r^2 into consideration). On the other hand, prediction of distal LAD stenosis was poor when CFR was measured in the LIMA, although LIMA flow type consideration greatly ameliorated its predictive capabilities. Finally, although statistically significant, LIMA flow type contributed very little to the prediction of distal LAD stenosis when CFR was measured in the LAD.

The time required to complete a CFR test (time for the acquisition of an adequate spectral Doppler signal of baseline coronary flow velocity plus 90-s adenosine infusion) was 7 ± 5 min (range 3 to 18 min) for the LIMA and 12 ± 5 min (range 5 to 29 min) for distal LAD.

Hemodynamic variables. Adenosine infusion induced similar hemodynamic changes in both LIMA and LAD CFR assessments. A slight increase in heart rate (from 68 ±

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Table 2. Prediction of Significant (≥70%) LIMA or Distal LAD Stenosis by LIMA and LAD Flow-Derived Indexes Using Transthoracic Doppler Ultrasound

	≥70% LAD Stenosis	≥70% LIMA Stenosis
Sensitivity (%)		
CFR LIMA (peak velocity)	42	12
CFR LAD (peak velocity)	91	0
SDPV LIMA ratio	21	0
DVTI LIMA fraction	0	1
Specificity (%)		
CFR LIMA (peak velocity)	93	100
CFR LAD (peak velocity)	100	93
SDPV LIMA ratio	78	82
DVTI LIMA fraction	97	56
Diagnostic accuracy (%)		
CFR LIMA (peak velocity)	72 (17.068)	64 (7.385)*
CFR LAD (peak velocity)	98 (85.312)	71 (1.662)*
SDPV LIMA ratio	61 (0.005)	24 (12.810)*
DVTI LIMA fraction	69 (2.781)	6 (30.967)*

Cut off values were: <2 vs. ≥2 for CFRs (13,16,18,19); >1 vs. ≤1 for SDPV LIMA ratio (2), and <0.5 vs. ≥0.5 for DVTI LIMA fraction (2). Next to the values of the diagnostic accuracy the corresponding chi-square values are reported, in parentheses. Direct comparison of these chi-square values may be performed between the two groups: *Significance ($p < 0.05$) of the difference is concluded for absolute chi-square differences ≥3.84 (1 degree of freedom). A similar method is useful for comparison among diagnostic accuracies.

Abbreviations as in Table 1.

13 to 76 ± 15 beats/min for LAD; and from 69 ± 14 to 77 ± 14 beats/min for LIMA) was counterbalanced by a slight decrease in mean arterial pressure (from 97 ± 6 to 89 ± 8 mm Hg for LAD; and from 97 ± 6 to 89 ± 4 mm Hg for LIMA). Baseline rate-pressure product was also similar and did not significantly change during adenosine infusion.

Adenosine infusion. Maximal increase in coronary flow velocity was obtained within 60 s of drug infusion, and flow returned to baseline within 30 s of discontinuing the drug. No major adverse reactions occurred during or after adenosine infusion. All patients experienced some degree of hyperventilation, which was marked in four and rapidly disappeared at the end of the infusion.

DISCUSSION

Selective coronary angiography is the gold-standard technique to evaluate graft function, but it cannot be routinely or serially used to assess modification in graft flow (22). Transthoracic Doppler echocardiography has been suggested as an alternative tool to explore LIMA flow at rest and stress (2–5,7,8), but previous reports were focused only on the diagnosis of LIMA obstruction, without taking into consideration the impact of downstream distal LAD stenosis and the influence of competitive flow from the native LAD.

In our patients with proximally occluded LAD and new distal LAD stenosis, CFR in the LIMA overestimated CFR in the distal LAD, failing to detect a significant LAD stenosis in 25% of the cases (Fig. 4), because low prelesional branch resistances might direct flow away from the stenosis (branch steal) (9).

In patients with flow competition between the LIMA and LAD, measurement of CFR in the distal LAD predicted the functional status of the LIMA-LAD conduit better than measurement in the graft alone, because competitive graft flow, irrespective of the presence of graft obstruction, blunts CFR in the LIMA but not in the LAD. The possible causes of blunted CFR in the LIMA in case of competitive flow with the native LAD are not known, but we may hypothesize that the angle between the graft and the LAD may facilitate flow in the native vessel. Competitive graft flow from the native LAD has been considered deleterious to the function of the LIMA-LAD conduit, as it may produce diffuse narrowing of the distal LIMA in approximately 10% of the patients (23,24). This belief has been subsequently revised, because it has been experimentally and clinically observed an adequate perfusion of the distal vessel, despite competitive flow and/or graft restricion (25,26). Our results confirm these findings. In fact, in our patients with competitive flow from the native LAD, a full-patent graft was more frequent (14 of 19 patients) than a diffusely narrowed graft (5 of 19 patients), and neither competitive flow from the native LAD nor graft obstruction affected CFR in the distal LAD.

Resting LIMA flow has been previously proposed for the identification of graft restriction or distal LAD stenosis (2,3,8,21). The resting flow pattern of the LIMA grafted over the LAD changes from arterial-like, with prominent systolic component, to coronary-like, with prominent diastolic component. According to previous reports, a prominent systolic component within the graft reflects increased resistance to flow in the arterial conduit, owing to distal LAD stenosis or graft restriction (2,3,8,21). This flow pattern was observed in most of our patients with graft flow competition from the native LAD, but only 5 of 19 had graft restriction and none had new distal LAD stenosis. Based on our results, abnormal resting LIMA flow indexes reflect more the presence of flow competition than graft restriction or coronary artery stenosis in the postanastomotic tract of the LAD. Conversely, in patients without competitive graft flow from the native LAD and new distal LAD stenosis, resting graft flow was often preserved.

Limitations. With the available technology, only the LIMA-LAD graft can be easily studied. In particular, LIMA flow is very easy to obtain, because the vessel is still, and Doppler sampling is less affected by wall motion artifact than the LAD. Further technological advances are needed to image other grafts, but with the concept clear in mind that distal recipient artery flow should be always sampled.

Conclusions. In patients with a proximally occluded LAD and patent LIMA, CFR in the distal LAD is more accurate for the detection of distal LAD stenosis than CFR in the LIMA. In patients with a proximally patent LAD and competitive flow, resting graft flow indexes are

Table 3. Variables Included in Multivariate Analysis to Predict Significant (≥70%) De Novo Stenosis in the Distal Left Anterior Descending Coronary Artery (Best Fit Linear Models: BMDP-9R)

Basal Covariates	Mean ± SD	Covariates Added to Basal Ones in Models A to D	Mean ± SD
Gender (male/female = 1/0)	0.875		
Age (yrs)	62 ± 8	LIMA CFR (units)	2.24 ± 0.89
Body surface area (m^2)	1.86 ± 0.14	LAD CFR (units)	2.55 ± 0.42
LVEDP (mm Hg)	13 ± 3	LIMA flow type	
Left ventricular ejection fraction (%)	56 ± 6	(1 = competitive vs. 0 = non-competitive)	0.197
Left ventricular wall motions score index	1.16 ± 0.22		
Baseline pressure-rate product	6690 ± 1372	Dependent variable	
Risk factors (present/absent = 1/0)	0.969		
SDPV LIMA ratio	0.99 ± 0.57	New distal LAD stenosis	
DVTI LIMA fraction	0.67 ± 0.11	(≥70% vs <70% = 1/0)	0.218

	Model A	Model B	Model C	Model D
Multiple r^2	0.552	0.207	0.564	0.395
F-statistics	57.24	8.02	39.69	70.09
DF_N	2	3	3	3
DF_D	93	92	92	92
Significance (p<)	0.0000	0.0001	0.0000	0.0000
Intercept ± SE	0.704 ± 0.23 (t = 3.06)	0.556 ± 0.220 (t = 2.53)	0.686 ± 0.228 (t = 3.00)	1.162 ± 0.145 (t = 7.98)

Entering Covariates	Age	LAD CFR	LVEDP	SDPV	LIMA CFR	Age	LAD CFR	LIMA Flow Type	Gender	LIMA CFR	LIMA Flow Type
Coefficient	0.0056	−0.327	0.021	−0.180	−0.194	0.0058	−0.316	−0.118	−0.189	−0.293	−0.602
SE	0.0034	0.031	0.012	0.070	0.045	0.0033	0.031	0.073	0.102	0.042	0.096
Stand. coeff.	0.114	−0.731	0.158	−0.248	−0.416	0.118	−0.706	−0.114	−0.152	−0.629	−0.580
T	1.64	−10.53	1.69	−2.56	−4.28	1.72	−10.01	−1.62	−1.85	−6.84	−6.26
p 2-tail	0.104	0.000	0.094	0.012	0.000	0.089	0.000	0.110	0.067	0.000	0.000
Tolerance	0.999	0.999	0.985	0.915	0.912	0.997	0.952	0.951	0.983	0.775	0.764
Contribution to r^2	0.013	0.533	0.024	0.056	0.158	0.014	0.474	0.012	0.022	0.307	0.257

Model A: Basal covariates plus LAD CFR; Model B: Basal covariates plus LIMA CFR; Model C: Basal covariates plus LAD CFR and LIMA flow type consideration; Model D: Basal covariates plus LIMA CFR and LIMA flow type consideration. Models A to D are different in that each one has a set of 10 basal covariates and either LAD or LIMA CFR, without (models A and B) or with (models C and D) LIMA flow type consideration. Thus models A and B have 11 covariates, whereas models C and D have 12 covariates. Direct comparison among models (taking DF_N and DF_D into account) may be performed considering that F-values ≥2.70 and 3.86 or ≥3.09 and 4.82 represent p values <0.05 and 0.01, respectively, for DF_N = 2 or 3 and DF_D = 100.

DF_D = denominator degrees of freedom; DF_N = numerator degrees of freedom; LVEDP = left ventricular end-diastolic pressure; SE = standard error; T = coefficient/SE; other abbreviations as in Table 1.

abnormal and CFR in the LIMA is blunted, but do not reflect downstream LAD flow, whereas CFR in the distal LAD does. Therefore, the non-invasive investigation of LIMA-LAD conduit by transthoracic Doppler ultrasound should be performed by measuring CFR in the distal LAD, whereas measurement in the graft alone may be misleading.

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REFERENCES

1. Loop FD, Lytle CM, Cosgrove DM, et al. Influence of the internal mammary artery graft of 10-year survival and other cardiac events. N Engl J Med 1986;314:1–6.
2. Crowley JJ, Shapiro LM. Noninvasive assessment of left internal mammary artery graft patency using transthoracic echocardiography. Circulation 1995;92 Suppl II:II25–30.
3. Takagi T, Yoshikawa J, Yoshida K, Akasaka T. Noninvasive assessment of left internal mammary artery graft patency using duplex Doppler echocardiography from the supraclavicular fossa. J Am Coll Cardiol 1993;22:1647–52.
4. Pezzano A, Fusco R, Child M, et al. Assessment of left internal mammary artery grafts using dipyridamole Doppler echocardiography. Am J Cardiol 1997;80:1603–6.
5. Calafiore A, Gallina S, Iacò A, et al. Minimally invasive mammary artery Doppler flow velocity evaluation in minimally invasive coronary operations. Ann Thorac Surg 1998;66:1236–41.
6. Voci P, Plaustro G, Testa G, Marino B, Campa PP. Visualizzazione delle arterie mammarie interne native e del graft aortocoronarico con ecocardiografia color-Doppler ad alta risoluzione. Cardiologia 1998; 43:403–6.
7. Katz WE, Zenati M, Mandarino WA, Cohen HA, Gorcsan G 3rd. Assessment of left internal mammary artery graft patency and flow reserve after minimally invasive direct coronary artery bypass. Am J Cardiol 1999;84:795–801.
8. Arruda AM, Pellikka PA, Mahoney DW, Joseph A Jr., Mathias W Jr., Seward JB. Transthoracic Doppler echocardiographic comparison of left internal mammary grafts to left anterior descending artery with ungrafted right internal mammary artery in patients with and without

myocardial ischemia by dobutamine stress echocardiography. Am J Cardiol 2000;86:919–22.
9. Gould KL, Kirkeeide RL, Buchi M. Coronary flow reserve as a physiologic measure of stenosis reverity. J Am Coll Cardiol 1990;15: 459–74.
10. Voci P, Testa G, Plaustro G. Imaging of the distal left anterior descending coronary artery by transthoracic color-Doppler echocardiography. Am J Cardiol 1998;81:74G–8G.
11. Voci P, Testa G, Plaustro G, Caretta Q. Coronary Doppler intensity changes during handgrip: a new method to detect coronary vasomotor tone in coronary artery disease. J Am Coll Cardiol 1999;34:428–34.
12. Voci P, Mariano E, Pizzuto F, Puddu PE, Romeo F. Coronary recanalization in anterior myocardial infarction: the open perforator hypothesis. J Am Coll Cardiol 2002;40:1205–13.
13. Hozumi T, Yoshida K, Ogata Y, et al. Noninvasive assessment of significant left anterior descending coronary artery stenosis by coronary flow velocity reserve with transthoracic color Doppler echocardiography. Circulation 1998;97:1557–62.
14. Caiati C, Montaldo C, Zedda N, Bina A, Iliceto S. New noninvasive method for coronary flow reserve assessment: contrast-enhanced transthoracic second harmonic echo Doppler. Circulation 1999;99:771–8.
15. Pizzuto F, Voci P, Mariano E, Puddu PE, Sardella G, Nigri A. Assessment of flow velocity reserve by transthoracic Doppler echocardiography and venous adenosine infusion before and after left anterior descending coronary stenting. J Am Coll Cardiol 2001;38:155–62.
16. Pizzuto F, Voci P, Mariano E, Puddu PE, Chiavari PA, Romeo F. Noninvasive coronary flow reserve assessed by transthoracic coronary Doppler ultrasound in patients with left anterior descending coronary artery stents. Am J Cardiol 2003;91:522–6.
17. Pizzuto F, Voci P, Mariano E, Puddu PE, Spedicato P, Romeo F. Coronary flow reserve of the angiographically normal left anterior descending coronary artery in patients with remote coronary artery disease Am J Cardiol 2004;94:577–82.
18. Heller LI, Cates C, Popma J, et al. Intracoronary Doppler assessment of moderate coronary artery disease: comparison with 201Tl imaging and coronary angiography. Circulation 1997;96:484–90.
19. Matsumura Y, Hozumi T, Watanabe H, et al. Cut-off value of coronary flow velocity reserve by transthoracic Doppler echocardiography for diagnosis of significant left anterior descending artery stenosis in patients with coronary risk factors. Am J Cardiol 2003;92: 1389–93.
20. Sugimoto S, Iwashiro K, Monti F, Dawodu AA, Schiariti M, Puddu PE. The risk of myocardial stunning is decreased concentration-dependently by K_{ATP} channel activation with nicorandil before K^+ cardioplegia. Int J Cardiol 1995;48:11–25.
21. Akasaka T, Yoshida K, Hozumi T, et al. Flow dynamics of the angiographically no-flow patent internal mammary artery graft. J Am Coll Cardiol 1998;31:1049–56.
22. Johnson LW, Krone R. Cardiac catheterization 1991: a report of a Registry of the Society for Cardiac Angiography and Intervention (SCA&I). Cathet Cardiovasc Diagn 1993;28:219–20.
23. Barner HB. Double internal mammary-coronary artery bypass. Arch Surg 1974;109:627–30.
24. Geha AS, Baue AE. Early and late results of coronary revascularization with saphenous vein and internal mammary artery grafts. Am J Surg 1979;137:456–63.
25. Lust RM, Zeri RS, Spence PA, et al. Effect of chronic flow competition on internal thoracic artery grafts. Ann Thorac Surg 1994;57:45–50.
26. Sabik JF 3rd, Lytle BW, Blackstone EH, et al. Does competitive flow reduce internal thoracic artery graft patency? Ann Thorac Surg 2003;761:1490–7.