

# Cardiac Events in Patients With Negative Maximal Versus Negative Submaximal Dobutamine Echocardiograms Undergoing Noncardiac Surgery

## Importance of Resting Wall Motion Abnormalities

Sherif B. Labib, MD, FACC, Michael Goldstein, MD, Paula M. Kinnunen, MD,  
Edgar C. Schick, MD, FACC

*Burlington, Massachusetts*

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<b>OBJECTIVES</b>	This study sought to evaluate the negative predictive value (NPV) of preoperative dobutamine stress echocardiography (DSE) in patients who fail to achieve target heart rate (HR) and assess the influence of resting wall motion abnormalities (WMAs) without demonstrable ischemia on perioperative events.
<b>BACKGROUND</b>	The prognostic value of a negative-submaximal DSE study before noncardiac surgery is unknown.
<b>METHODS</b>	Consecutive patients (n = 429) who underwent surgery over a three-year period, preceded by DSE, were included. We compared perioperative event rates among those without inducible ischemia according to whether or not 85% age-adjusted maximum HR was achieved, and whether WMAs were present at rest.
<b>RESULTS</b>	Of 397 negative DSEs, peak HR was <85% maximum predicted in 62 (16%). Most were receiving beta-blockers (77%). The average dobutamine and atropine doses were 48 $\mu\text{g}/\text{kg}/\text{min}$ and 1.2 mg, respectively. Average HR was 115 beats/min (74% maximum predicted). Perioperative myocardial infarctions occurred more frequently in patients with positive tests (3 of 32 [9.4%] vs. 7 of 397 [1.8%]; $p = 0.03$ ), but with similar frequency among the negative-maximal and negative-submaximal groups (6 of 335, 1.8% vs. 1 of 62, 1.6%, respectively). Accordingly, the NPV was 98% in both subgroups. Events occurred exclusively in patients with WMAs at rest: 7 of 100 (7%) versus 0 of 297 (0%) ( $p < 0.0001$ ).
<b>CONCLUSIONS</b>	In patients undergoing preoperative DSE, failure to achieve target HR is not uncommon despite an aggressive DSE regimen. A negative DSE without resting WMAs has excellent NPV regardless of the HR achieved. Patients with resting WMAs appear to be at increased risk for perioperative events even without provokable ischemia. (J Am Coll Cardiol 2004; 44:82-7) © 2004 by the American College of Cardiology Foundation

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Dobutamine stress echocardiography (DSE) is widely used for preoperative evaluation of ischemic risk in patients with known or suspected coronary artery disease (CAD). The presence of inducible ischemia has been consistently shown to be a potent independent predictor of postoperative cardiac events in patients undergoing major vascular (1-5) and nonvascular surgery (6-8). The absence of ischemia, on the other hand, is associated with excellent outcomes.

Despite high-dose dobutamine plus atropine, it is not always possible to achieve the commonly applied diagnostic goal of 85% age-adjusted maximum predicted heart rate (HR), which appears to optimize test sensitivity (9,10). The outcome in patients with suboptimal HR response during DSE in the perioperative setting is not known. The objective of this study was to evaluate the negative predictive value (NPV) of submaximal DSE for assessment of cardiac risk before vascular and nonvascular surgery by comparing

perioperative cardiac events in patients who have a negative-submaximal DSE with those who have a negative-maximal DSE. We also sought to determine the prognostic significance of a wall motion abnormality (WMA) present at rest in the absence of inducible ischemia.

## METHODS

**Patients.** Consecutive DSEs performed between 1998 and 2001 at the Lahey Clinic for preoperative evaluation in patients with known or suspected CAD, who were not anticipated to perform adequate treadmill exercise, were screened. Medical records of those with and without inducible ischemia who subsequently underwent major surgery within six months of the DSE were reviewed. Patients' records were analyzed for the presence of conventional risk factors, type of surgery performed, cardiac catheterization or revascularization, and perioperative cardiac events. History of CAD included treatment for angina pectoris, clinical myocardial infarction (MI), angiographically documented coronary obstruction, or previous coronary revascularization. Beta-blockers were not routinely omitted before DSE and

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From the Department of Cardiovascular Medicine, Lahey Clinic, Burlington, Massachusetts.

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#### Abbreviations and Acronyms

CAD	= coronary artery disease
DSE	= dobutamine stress echocardiography
HR	= heart rate
MI	= myocardial infarction
NPV	= negative predictive value
WMA	= wall motion abnormality

were continued perioperatively in patients who were taking them at the time of DSE.

**DSE.** Parasternal long- and short-axis, apical four- and two-chamber views were obtained at baseline and at the end of each 3-min stage. Images were digitally stored at baseline, low dose, peak infusion, and recovery, and were also recorded on videotape. Blood pressure and 12-lead electrocardiogram were also obtained after each 3-min stage. Dobutamine was administered intravenously with an infusion pump starting at 5  $\mu\text{g}/\text{kg}/\text{min}$ . and advanced every 3 min to 10, 20, 30, 40, and 50  $\mu\text{g}/\text{kg}/\text{min}$ . Supplemental atropine was administered intravenously in 0.25-mg increments up to a maximum dose of 2.0 mg, as required to achieve target HR, defined as at least 85% of maximum predicted HR based on age (maximum age-predicted HR =  $220 - \text{age}$ ). The test was terminated when the target HR was attained, after completion of drug infusion protocol, or when objective evidence of ischemia became apparent. Patients in whom the protocol was prematurely terminated (dobutamine dose  $<30 \mu\text{g}/\text{kg}/\text{min}$ ) due to intolerable side effects, including excessive hypotension or hypertension, were excluded from analysis.

**Patient subgroups according to DSE results.** Dobutamine stress echocardiography was considered "positive" for ischemia if a new or worsening WMA was identified with dobutamine. Included in this group were patients with a resting WMA who exhibited initial improvement in contractility with low-dose dobutamine but deterioration at higher-dose (biphasic response). The DSE was considered "negative" for ischemia if no new WMAs were identified, or a baseline WMA did not worsen. For analysis, the negative group was first divided according to achievement of 85% maximum-predicted HR for age (i.e., negative-maximal vs. negative-submaximal); a second comparison was based on the presence or absence of a WMA at rest (i.e., negative-normal vs. negative-fixed).

**Cardiac events.** In-hospital perioperative cardiac events (MI or cardiac death) were compared in the different patient groups. The diagnosis of MI was based on creatine kinase elevation  $>194 \text{ IU/l}$  with MB index of 5% or greater, or Troponin I  $>2.0 \text{ mg/ml}$  during hospitalization. These were measured serially in patients who experienced angina, demonstrated ECG abnormalities, congestive heart failure, significant arrhythmia, or hemodynamic instability. Cardiac revascularization procedures performed as a result of abnormal DSE result were also tracked.

**Statistical analysis.** Continuous variables are presented as mean  $\pm$  SD, and statistical comparisons utilized unpaired Student *t* test. Categorical variables are expressed as percentages, and differences were compared using chi-square with two-tailed *p* values. Fisher exact test was used if the number in any cell was  $<5$ , which was the case in all cardiac event analyses. A *p* value of  $<0.05$  was considered statistically significant. Logistic regression was used to determine odds ratios and 95% confidence intervals, for one or two predictors at a time. Analyses were performed using SPSS software (SPSS Inc., Chicago, Illinois). Negative predictive value was calculated in the standard fashion.

## RESULTS

**Patient characteristics and DSE findings.** Of 606 preoperative DSEs reviewed, 166 were excluded because the patient did not undergo surgery within six months of the DSE, including 54 patients with inducible ischemia. Ten patients, two of whom sustained a postoperative MI, were excluded from analysis because of premature discontinuation of DSE protocol. Preoperative DSE was terminated in both patients at 20- $\mu\text{g}/\text{kg}/\text{min}$  dose without use of atropine because of a persistent marked elevation in blood pressure. Peak HR was  $<90$  beats/min in both. One patient was excluded because of noncardiac death one week postoperatively. The remaining 429 patients, who represented the study group, comprised 32 patients with, and 397 without, inducible ischemia.

Among patients without inducible ischemia despite completion of the dobutamine-atropine protocol, the prevalence of submaximal HR was 62 of 397 (15.6%), and the prevalence of a fixed WMA was 100 of 397 (25.2%). When categorized according to percent of age-predicted maximum HR, the negative-submaximal group comprised 16 patients achieving  $<70\%$ , 37 patients achieving 71% to 80%, and 9 patients achieving 81% to 84%. In contrast with the negative-maximal group, the negative-submaximal group had lower HR in absolute terms ( $115 \pm 14$  beats/min vs.  $135 \pm 11$  beats/min;  $p < 0.0001$ ), as well as percent of age-predicted maximum HR achieved ( $74 \pm 7\%$  vs.  $90 \pm 9\%$ ;  $p < 0.0001$ ), after receiving higher doses of dobutamine ( $48 \pm 4 \mu\text{g}/\text{kg}/\text{min}$  vs.  $40 \pm 9 \mu\text{g}/\text{kg}/\text{min}$ ;  $p < 0.0001$ ) and atropine ( $1.2 \pm 0.6 \text{ mg}$  vs.  $0.27 \pm 0.4 \text{ mg}$ ;  $p < 0.0001$ ).

The baseline characteristics and DSE findings of the negative DSE groups are presented in Table 1. In contrast with the negative-maximal group, the negative-submaximal group was younger ( $65 \pm 13$  years vs.  $70 \pm 11$  years;  $p = 0.002$ ), included more patients with an established history of CAD (48.4% vs. 28.7%;  $p = 0.003$ ), congestive heart failure (10% vs. 4%,  $p = 0.046$ ), and patients receiving beta-blockers (77.4% vs. 40%;  $p < 0.0001$ ). In contrast with the negative-normal group, the negative-fixed group contained more patients with an established history of CAD (50.0% vs. 25.6%;  $p < 0.0001$ ), congestive heart failure (12.0% vs. 2.0%;  $p < 0.0001$ ), and more patients receiving beta-

**Table 1.** Baseline Characteristics and DSE Results in 397 Patients Without Inducible Ischemia and the Subgroups

	Entire Negative Group	Negative DSE Subgroups					
		Submaximal	Maximal	p Value	Normal	Fixed WMA	p Value
Patients	397	62	335	N/A	297	100	N/A
Age	69 ± 10	65 ± 13	70 ± 11	0.002	68 ± 12	71 ± 10	0.08
Male (%)	233 (59)	35 (56)	198 (59)	0.80	159 (54)	74 (74)	<0.001
Diabetes (%)	96 (24)	14 (23)	82 (24)	0.87	65 (22)	31 (31)	0.08
CAD (%)	126 (32)	30 (48)	96 (28)	0.003	76 (26)	50 (50)	<0.0001
CHF (%)	18 (5)	6 (10)	12 (4)	0.046	6 (2)	12 (12)	<0.0001
Beta-blocker (%)	180 (45)	48 (77)	132 (40)	<0.0001	117 (39)	63 (63)	<0.0001
HR	131 ± 14	115 ± 14	135 ± 11	<0.0001	132 ± 14	128 ± 13	0.012
% MPRH	87 ± 10	74 ± 7	90 ± 9	<0.0001	87 ± 10	86 ± 9	0.64
Rest WMA (%)	100 (25)	21 (34)	79 (24)	0.11	0	100	N/A
Rest EF	58% ± 10	58% ± 9	58% ± 10	0.95	62% ± 5	46% ± 13	<0.001
Vascular surgery (%)	121 (30)	30 (48)	91 (27)	0.001	78 (26)	43 (43)	0.002

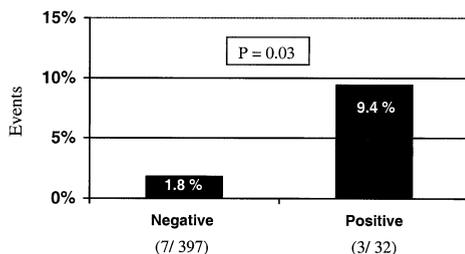
CAD = known history of coronary artery disease; CHF = history of congestive heart failure; DSE = dobutamine stress echocardiogram; EF = ejection fraction; HR = heart rate; % MPRH = percent of maximum predicted heart rate for age; N/A = not applicable; WMA = wall motion abnormality.

blockers (63% vs. 39%;  $p < 0.0001$ ). Compared with the negative group as a whole, patients in the “positive” ischemia group had higher prevalence of known CAD (64% vs. 32%;  $p = 0.0008$ ), resting WMA (54% vs. 25%;  $p = 0.003$ ), and use of beta-blockers (75% vs. 45%;  $p = 0.002$ ). There was no significant difference in the other baseline characteristics or in the proportion of patients undergoing vascular surgery.

**Surgical procedures.** In the group of 397 patients with negative DSE, vascular surgery was the most common procedure (121 patients, 30%); of these, 41% were repairs of abdominal aortic aneurysm. Orthopedic surgery was performed in 73 patients (18%); intra-abdominal or colon surgery in 70 patients (18%); urologic surgery in 36 patients (9%); intra-thoracic surgery in 26 patients (7%); neurosurgery in 26 patients (7%); and miscellaneous surgeries in 45 patients (11%)

**Cardiac events.** Of the 32 patients with a positive preoperative DSE, 7 of 32 (21.9%) suffered an acute MI (3 patients) or underwent preoperative revascularization as a result of the DSE findings (4 patients). None of the patients revascularized sustained an MI at subsequent surgery. The perioperative MI rate among patients with a negative DSE was 7 of 397 (1.8%), which was significantly lower than that associated with ischemia (3 of 32 or 9.4%),  $p = 0.03$  (Fig. 1).

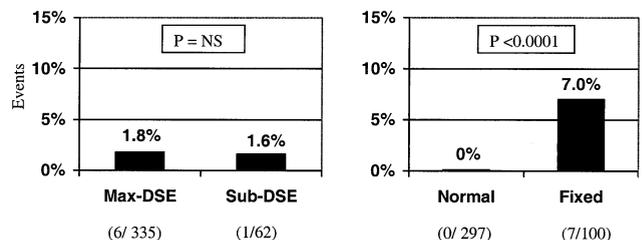
Among the 397 patients with negative DSE, six events occurred in the negative-maximal DSE subgroup (335



**Figure 1.** Cardiac event rates (myocardial infarction or death) in patients with negative versus positive dobutamine stress echocardiography. Those without inducible ischemia had significantly fewer cardiac events.

patients), and one in the negative-submaximal subgroup (62 patients). Thus, event rates in the submaximal and maximal subgroups were similar (1.6% vs. 1.8%, respectively;  $p = 1.0$ ) as shown in Figure 2 (left panel). The event rate in the negative-submaximal subgroup (1.6%) was lower than that of the inducible ischemia group when a composite event rate of perioperative MI or revascularization is considered (21.9%;  $p = 0.002$ ). When examined according to beta-blocker use, the event rate among patients receiving beta-blocker at time of surgery was 4 of 180 (2.2%) versus 3 of 217 (1.4%) ( $p = NS$ ). The similarity in event rates may relate to the higher prevalence of established history of CAD and WMAs among patients who received beta-blockers than those who did not (77 of 180, 42.8% vs. 49 of 217, 22.6%;  $p < 0.001$ , and 63 of 180, 35.0% vs. 37 of 217, 17.1%;  $p < 0.001$ , respectively).

When examined according to the presence of WMA at rest, event rate in the negative-fixed WMA subgroup 7 of 100 (7%) was significantly higher than the negative-normal subgroup (0 of 297 or 0%);  $p < 0.0001$ , as shown in Figure 2B. In an attempt to examine predictors of events, the odds ratio of the baseline characteristics and echocardiographic variables among patients with a negative DSE was calculated (Table 2). The following variables were significantly



**Figure 2.** Cardiac event rates among the 397 patients without inducible ischemia. The left panel shows events according to whether target heart rate was achieved during dobutamine stress echocardiography (DSE) (Max-DSE) or not (Sub-DSE). Event rates were low in both subgroups. The right panel shows events according to whether patients had normal resting wall motion (Normal) or had a wall motion abnormality at rest (Fixed). Those with a fixed wall motion abnormality had significantly higher event rates. There were no events in patients with normal baseline function and no inducible ischemia.

**Table 2.** Predictors of Postoperative Cardiac Events (MI, Death) in 397 Patients Without Inducible Ischemia During DSE Testing

	No Event n, %	Event n, %	p Value	Odds Ratio	95% Confidence Interval
Age ≥70 yrs	216 (55)	3 (43)	0.705	0.60	(0.13-2.7)
Male	226 (58)	7 (100)	0.045	NA*	
Diabetes	92 (24)	4 (57)	0.062	4.31	(0.95-19.65)
CAD	121 (31)	5 (71)	0.035	5.56	(1.06-29.05)
CHF	18 (5)	0 (0)	1.00	NA*	
Beta-blocker	176 (45)	4 (57)	0.706	1.62	(0.36-7.3)
Submaximal DSE	61 (16)	1 (14)	1.00	0.90	(0.11-7.6)
Vascular surgery	117 (30)	4 (57)	0.207	3.11	(0.69-14.1)
Rest WMA	93 (24)	7 (100)	<0.001	NA*	
Rest EF <35%	11 (3)	2 (29)	0.019	13.78	(2.41-78.99)

\*Odds ratios could not be computed when 0% or 100% of events occurred in one group.  
 MI = myocardial infarction. Other abbreviations as in Table 1.

associated with an event based on Fisher exact test: male gender, history of CAD, resting WMA, and ejection fraction <35%.

The NPV of DSE was 98%, whether or not 85% maximum predicted HR was achieved. When results were examined according to the presence of WMA at rest, the NPV in the normal and fixed subgroups was 100% and 93%, respectively.

## DISCUSSION

Our data suggest that a negative-submaximal DSE, which is traditionally considered nondiagnostic, has useful prognostic value in the perioperative setting, and that despite lack of inducible ischemia, perioperative events occurred with greater frequency in patients with a fixed WMA than those without a resting WMA. To our knowledge, this is the first study to specifically examine perioperative outcome in those two subgroups. Despite completion of a high-dose dobutamine and atropine protocol, a substantial minority of patients (16%) with a negative test did not attain target HR. The event rate in this negative-submaximal subgroup was 1.6%, which is comparable to the event rate in the negative-maximal subgroup (1.8%). Thus, the NPV of a submaximal test remains high (98%), and is the same as that of a negative-maximal DSE. When event rates in the negative dobutamine group are examined according to the presence or absence of a resting WMA, those with normal wall motion at rest and a negative DSE had a significantly lower event rate than those with fixed WMA (0% vs. 7.0%, respectively;  $p < 0.0001$ ). Thus, the NPV of a normal DSE without resting or dobutamine-induced WMA is 100% in this study.

The higher perioperative event rate among patients with inducible ischemia on DSE than those without in this study (9.4% vs. 1.8%,  $p = 0.03$ ) and the high NPV (98%) are consistent with previous DSE reports (1-8) and dipyridamole thallium studies (96% to 100%) (8,11).

**Submaximal studies and ischemic threshold.** Use of 85% maximum predicted HR as a target to optimize the diagnostic performance of exercise stress tests is based on

observations of improved sensitivity in detection of coronary obstruction in angiographic correlations studies (12,13), and poor functional capacity has been shown to be an independent predictor of poor outcome (14). In exercise-based stress testing for preoperative evaluation, inability to achieve adequate HR is associated with worse outcome (15). Accordingly, current guidelines recommend coronary angiography for selected patients with nondiagnostic or equivocal noninvasive tests who are undergoing high-risk surgical procedures (8). Contrary to this convention, the NPV of a negative-submaximal DSE in our study was high and nearly identical to that of a negative-maximal DSE test.

There are two potential explanations for the relatively low perioperative event rate in the submaximal DSE subgroup observed in this study. In contrast with exercise-based stress testing, failure to obtain 85% maximum predicted HR despite maximal dobutamine-atropine stimulation is not necessarily indicative of poor functional capacity, or inadequate cardiopulmonary reserves, and may, in fact, imply decreased liability to perioperative ischemia, even if un-revascularized coronary disease is present. A large proportion of patients in the submaximal DSE subgroup were receiving beta-blockers (77%), and inability to attain 85% maximum predicted HR may, to an extent, be a marker of an effective degree of beta-blockade. Blunting of the expected tachycardic response to major surgery, which decreases the likelihood of prolonged ischemia in the perioperative period, is thought to be one of the mechanisms by which beta-blockers confer their protective effect (16,17).

Another, although less likely, explanation is that patients in the negative-submaximal group have a low prevalence or less severe degree of CAD that was correctly identified by the DSE despite the submaximal HR. However, many of the patients in the submaximal subgroup had known history of CAD (48%); thus, it is unlikely that these patients somehow represent an unusually low-risk group.

**Pre-existing WMAs.** The event rate in our study was markedly influenced by the presence or absence of a WMA at rest. In the 397 patients without inducible ischemia, events occurred without exception in those with a pre-

existing WMA. There were no events in the 297 patients with normal resting wall motion regardless of whether or not target HR was achieved during DSE. As a result, the NPV of a negative-normal DSE (maximal or submaximal) was 100%.

The event rate in the subgroup with a fixed WMA, on the other hand, was surprisingly high (7.0%) in the absence of inducible ischemia. The detection of ischemia on preoperative stress testing identifies patients who are at an increased risk for cardiac events arising from prolonged supply-demand imbalance related to factors such as postoperative fever, anemia, tachycardia, or hypotension. Many perioperative infarctions, however, occur when no such imbalance is apparent, and are mediated by plaque rupture and thrombosis, in the context of intensified postoperative inflammatory or hypercoagulable state (18,19). Such a mechanism may elude preoperative detection if the culprit plaque is nonobstructive. In the nonoperative setting, approximately two-thirds of MIs are caused by rupture of hemodynamically insignificant plaques (20). In the perioperative setting, nonobstructive lesions at angiography were found to be associated with MI and death (21), and, in autopsy-based studies, approximately one-half of fatal postoperative MI cases were associated with plaque rupture (22,23). The presence of a fixed WMA identifies patients who have underlying CAD who may be at risk for plaque rupture and consequent MI even in the absence of obstructive disease preoperatively.

An alternative explanation for the increased event rate associated with a fixed WMA is reduced sensitivity of echocardiography for detection of ischemia superimposed on a resting WMA, which could lead to underestimation of ischemia. Up to one-third of segments exhibiting echocardiographically fixed WMAs have partially reversible perfusion defects by nuclear imaging (24,25). In viability studies in the setting of left ventricular dysfunction, it has been suggested that DSE has lower sensitivity (and higher specificity) than thallium in detecting ischemic but viable myocardium (26,27).

Although not previously emphasized, our finding of increased risk for cardiac events with a resting WMA is not unprecedented. A higher event rate associated with a fixed WMA on DSE has been previously demonstrated in several large studies in settings unrelated to surgery (28-31). In one study of 860 patients, the event rate in patients with a fixed WMA was significantly higher than those with normal DSE, and comparable with the rate in patients with inducible ischemia (29). Increased postoperative cardiac complications related to fixed perfusion defects have been observed in several nuclear imaging-based studies, with an almost threefold increase in perioperative risk reported in a meta-analysis report (11). The association between fixed WMA on DSE and outcome in the perioperative setting observed in the present study has not been made previously. This observation is particularly pertinent clinically if there is a tendency to overlook a fixed WMA result and make a risk

assessment based primarily on the presence or absence of "ischemia," as defined by a new or worsening WMA.

**Study limitations.** The small number of events in our study of patients with a negative DSE makes it difficult to interpret differences between subgroups. Laboratory screening for perioperative MI was not routinely carried out in all patients in this retrospective study, but only as clinically indicated, and events may have been underestimated. However, the intent of the study was to evaluate clinically significant events; it is unlikely that these would have occurred without clinical manifestations. The surgical procedures included both vascular as well as nonvascular surgeries, and may not be as uniform as in other studies that focused on a single surgical category. Our study does, however, reflect the heterogeneity commonly encountered in clinical practice. It is important to note that the high NPV of a negative-submaximal DSE we observed is predicated upon the completion of the dobutamine-atropine protocol; thus the findings should not be extrapolated to those who do not complete the relatively aggressive regimen employed in our study. Finally, one of the important goals of preoperative evaluation is long-term risk assessment, which is not addressed in our study.

**Conclusions.** Failure to achieve the target HR of 85% of maximum predicted for age is not uncommon despite a high dose dobutamine and atropine protocol. In patients undergoing major noncardiac surgery, a negative DSE without resting WMAs has excellent NPV regardless of whether or not the target HR is achieved. Patients with resting WMAs appear to be at a substantially higher risk for perioperative events despite the absence of an ischemic response.

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**Reprint requests and correspondence:** Dr. Sherif B. Labib, Department of Cardiovascular Medicine, Lahey Clinic, 41 Mall Road, Burlington, Massachusetts 01805. E-mail: sherif.b.labib@lahey.org.

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