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Changes in Regional Myocardial Function after Coronary Artery Bypass Graft Surgery Are Predicted by Intraoperative Low-dose Dobutamine Echocardiography

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Background: **Left ventricular dysfunction is often reversed after coronary artery bypass graft (CABG) surgery; however, this change is not easily predicted. The authors hypothesized that functional changes after a low dose of dobutamine (5 μg · kg^{-1} · min^{-1}) intraoperatively would predict functional changes when complete revascularization was achieved.**

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Methods: **The authors analyzed 560 segments in 40 patients scheduled for elective CABG surgery for regional wall motion (1–5 scoring system) at four stages: baseline (after induction and intubation), with administration of low-dose dobutamine before cardiopulmonary bypass, after separation from cardiopulmonary bypass (early), and after administration of protamine (late). Two independent observers scored the myocardial regions according to a 16-segment model in multiple imaging planes. For each segment, the response to dobutamine was dichotomized as improved or not improved from baseline and analyzed with logistic regression. The influence of covariates (ejection fraction, myocardial infarction, diabetes mellitus, and β blockers) was also determined with logistic regression models. $P < 0.05$ was considered significant.**

Results: **Changes in myocardial function after low-dose dobutamine were highly predictive for early ($P < 0.0001$) and late ($P < 0.0001$) changes in myocardial function from baseline regional scores. The overall odds ratio for early and late improvement increased by 20.7 and 34.6, respectively, when improvement was observed after low-dose dobutamine was administered. The overall positive predictive value of improved regional wall motion after CABG did not vary with left ventricular ejection fraction, a history of myocardial infarction, or β blocker use, and it varied little with diabetic status (range, 0.86–0.96) if regional wall motion improved with low-dose dobutamine before CABG. The overall negative predictive value was 0.70; however, the range varied with diabetic status (*i.e.*, lowest in diabetic patients and highest in nondiabetic patients).**

Conclusion: **Intraoperative low-dose dobutamine is a reliable method to predict myocardial functional reserve and to determine functional recovery expected after coronary revascularization. (Key words: Cardiac function; revascularization.)**

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LEFT ventricular dysfunction in patients with chronic ischemic heart disease is not necessarily irreversible, and myocardial dysfunction is often reversed after coronary bypass surgery.[1–4] However, the changes expected in regional function after coronary artery bypass graft (CABG) surgery are not easily predicted before revascularization by assessment of baseline function with angiography or echocardiography.[3–6]

During surgery for ischemic heart disease, it is critical to distinguish dysfunctional but viable myocardial regions from dysfunctional and nonviable regions because prognosis and therapeutic strategies depend on understanding the difference between reversible and nonreversible dysfunction. Likewise, an evaluation of the adequacy of revascularization during surgery depends on the ability to predict changes in the flow–function dynamic immediately after surgery.[7] Factors unique to coronary revascularization may confound assessment of changes in regional function after surgery when one tries to evaluate the "adequacy of repair."[8–10]

We used an intraoperative low-dose dobutamine stimulation test after induction of anesthesia and before coronary revascularization to predict changes in regional function after CABG. We hypothesized that changes observed in regional function after administration of low-dose dobutamine represent a gold standard of functional changes to expect after successful revascularization. Experimental evidence and clinical use have confirmed that low-dose dobutamine increases coronary blood flow and contractility without an associated increase in regional myocardial oxygen demand.[11–13]

The purpose of this study was to test the hypothesis that intraoperative low-dose dobutamine echocardiography would predict functional recovery after CABG at the time of surgery. We also sought to evaluate the utility of this method for defining a standard of regional function changes to expect when coronary revascularization is completed.

Methods

After obtaining institutional review board approval, we prospectively studied 40 patients with angiographic documentation of multivessel coronary artery disease who were scheduled for elective coronary bypass surgery. Informed consent was obtained from all subjects. Patients were excluded from participating in the study if they were younger than 18 yr, refused to give written informed consent, or were hemodynamically unstable and receiving exogenous (pharmacologic or mechanically assisted) circulatory support at the time of anesthesia induction.

Preoperative history, physical examination, and diagnostics were recorded, including medications; left ventricular ejection fraction; data from angiography, preoperative echocardiography, and thallium perfusion; electrocardiogram; history of diabetes mellitus; renal insufficiency; a previous myocardial infarction; hypertension; and planned operation.

General anesthesia was maintained in all patients with isoflurane (1.0–3.0%), fentanyl (10–20 μg/kg), and pancuronium (1 mg/kg). Cardiopulmonary bypass (CPB) was conducted with a single two-stage venous cannula and a single aortic cross-clamp. Cold blood–crystallatoid (4:1) cardioplegia was delivered antegrade for 2 min (500 ml/min) and retrograde (250 ml/min) for 2 min to induce cardioplegic arrest. The temperature was allowed to drift to 32°C during CPB with flow maintained at 2.4 $l \cdot min^{-1} \cdot m^{-2}$ until 34°C. Then flow was maintained at 2.0 $l \cdot min^{-1} \cdot m^{-2}$. After induction of general anesthesia and intubation, all subjects underwent a complete basic transesophageal echocardiography examination[14] (Acuson Sequoia, Mountain View, CA, or Hewlett Packard 5500, Andover, MA) with an omniplane probe. Particular focus was directed to record a multiple segment analysis of the left ventricle with images obtained in the midesophageal four-chamber view, midesophageal two-chamber view, midtransgastric short-axis view, midtransgastric two-chamber view, and the midesophageal long-axis view (fig. 1). Next, a low-dose infusion (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) of dobutamine was begun, and, after 5 min, images were again recorded. Images were recorded in a similar manner immediately on separation from CPB and 30 min after the administration of protamine. Vital signs, including heart rate, rhythm, blood pressure, pulmonary artery pressure, and central venous pressure, were recorded at each imaging interval. Criteria for stopping the dobutamine infusion were hypotension, significant ventricular or supraventricular arrhythmias, or a new or worsened abnormality in regional wall motion (RWM) in at least two segments.

Recorded images were digitally stored in loop formation with electrocardiogram R-wave triggering to capture a representative cardiac cycle in each view at 30 frames/s. The first 450 ms of the selected cycle was displayed in a continuous loop in quad-screen format to evaluate changes in RWM and systolic wall thickening. Two observers independently compared all images simultaneously at each stage (baseline, low-dose dobutamine, after CPB, and after protamine) in each view. Systolic wall thickening and RWM abnormality were assessed accordingly to the following scale: 1 = normal, 2 = mild hypokinesia, 3 = severe hypokinesia, 4 = akinesia, 5 = dyskinesia, 0 = unable to image. A region was assigned a score of 0 only if both the digitally recorded clips and analog (video) recorded images did not provide an adequate image to grade. An RWM score was assigned to each segment at each stage by each observer. Redundant segments in different image planes

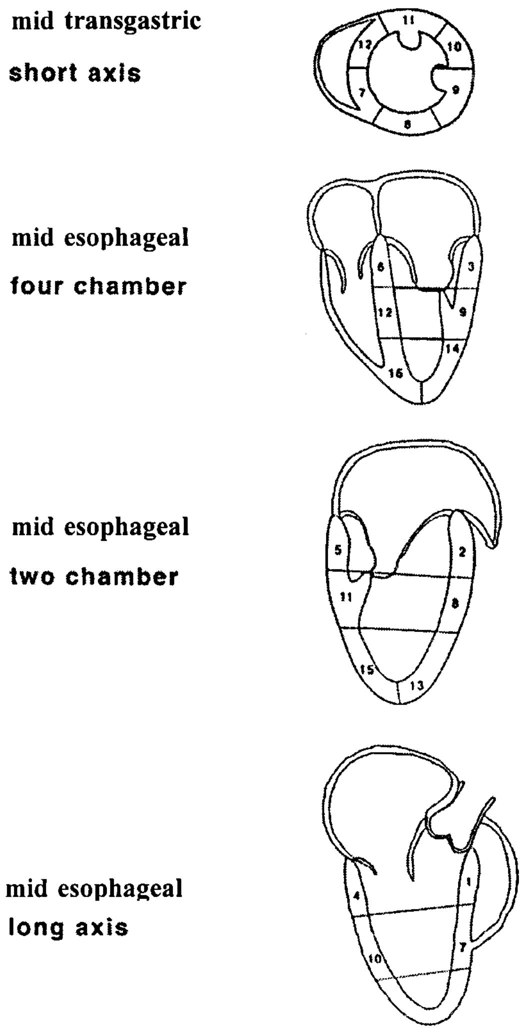

Fig. 1. Basal segments: 1 = basal anteroseptal; 2 = basal anterior; 3 = basal lateral; 4 = basal posterior; 5 = basal inferior; 6 = basal septal. Mid segments: 7 = mid anteroseptal; 8 = mid anterior; 9 = mid lateral; 10 = mid posterior; 11 = mid inferior; 12 = mid septal. Apical segments: 13 = apical interior; 14 = apical lateral; 15 = apical inferior; 16 = apical septal.

were not scored twice, and the segment in the midtransgastric short-axis view was recorded. If there was disagreement between observers, a third score was sought from another observer who was blinded to the scores of the first two. The final score was derived by consensus of all three observers when there was disagreement. Interobserver and intraobserver variation in scoring was determined. Contractile reserve was considered present if RWM improved at low-dose dobutamine infusion. Surgical revascularization was considered successful if RWM after CABG was similar to RWM before CABG but after dobutamine infusion. For the purposes of this study, we assumed that all abnormal segments at rest before dobutamine infusion that improved after dobutamine infusion were hibernating, unless there was specific evidence from history to the contrary, such as acute myocardial ischemia reperfusion. If abnormal segments did not improve after low-dose dobutamine, they were considered infarcted, and there was no expectation for improvement in regional contraction patterns from surgical revascularization. Segments that were normal before dobutamine infusion and either normal or hyperkinetic after were expected to remain normal after CABG. Data were analyzed using the generalized estimating equation extension of logistic regression,[15] which incorporates correlation among segments of the same patient into the model. Positive and negative predictive values were computed from these models. Analyses were performed using the GENMOD procedure in SAS statistical analysis software.[16]

** The data are presented on the Internet Web site for this manuscript.

Results

Fourteen segments were scored in each patient at each stage; therefore, 560 segments in 40 patients were analyzed at four different stages: baseline, low-dose dobutamine, early separation from CPB, and late separation from CPB (2,240 segments total). The midesophageal long-axis view was not acquired in all patients, and thus segments unique to this view were eliminated from the overall analysis.

The average age among the patients enrolled was 63.3 ± 9.7 yr (range, 43–80 yr). There were 29 men and 11 women, of whom 20 had diabetes, 19 were taking β blockers, and 24 had a preoperative left ventricular ejection fraction $> 45\%$. RWM was always analyzed without inotropic support. Other data regarding angiographic evidence of coronary artery disease, surgical procedure, preoperative medications, preoperative assessment of global ventricular function, and coronary flow reserve for each patient were recorded.**

Overall, low-dose dobutamine was a highly significant predictor for early and late changes in myocardial function after CABG ($P < 0.0001$), with a positive predictive value range of 0.86–0.96. The probability of having an improved score at 5 min (early) after CABG if there was an improvement after low-dose dobutamine was 0.88. The positive predictive value of low-dose dobutamine

Table 1. The Overall Positive Predictive Value and Negative Predictive Value of Regional Changes after Low–Dose Dobutamine in All Segments Analyzed

	Positive Predictive Value	Negative Predictive Value
Changes in early phase	0.88	0.70
Change in late phase	0.94	0.70

was greater for late than for early functional changes (table 1). Response to dobutamine was a highly significant predictor of improvement at the time of immediate separation from CPB, independent of patient and surgical covariates. Ignoring covariates and given improvement with dobutamine, there was approximately a 20-fold increase in the likelihood of improvement from baseline at the early phase (odds ratio [OR] = 20.7; 95% confidence interval [CI] = 7.57, 56.6). Adjusting for diabetic status, the likelihood of improvement in nondiabetic patients increased more than 40-fold (OR = 43.33; 95% CI = 21.89, 85.75; $P \leq 0.0001$) compared with a sevenfold increase (OR = 7.46; 95% CI = 2.95, 18.55; $P < 0.0001$) in diabetic patients. Given improvement with dobutamine, the probability of having an improved score at 30 min after protamine administration was 0.94. Response to dobutamine was a highly significant predictor of improvement at the late phase, independent of left ventricular ejection fraction, history of myocardial infarction, and β blocker use. The effect of the response to dobutamine was independent of diabetic status. Segments that responded to dobutamine were approximately 35 times more likely to improve at the late phase than those that did not respond to dobutamine (OR = 34.6; 95% CI = 17.64, 6.74; $P \leq 0.00001$). Segments of patients with diabetes were approximately two times more likely to improve than segments of nondiabetic patients (OR = 2.17; 95% CI = 1.01, 4.63). Negative predictive values were lower overall than positive predictive values and were lowest for segments of diabetic patients (tables 1 and 2).

Among the 560 segments analyzed at baseline, 291 were abnormal (baseline score > 1), and 205 segments improved after dobutamine, including 101 that reverted to normal. One segment became progressively worse compared with baseline function. After CABG, 174 of the 205 segments remained at their functional state after dobutamine at early CPB separation, and 189 of 205 improved to their functional state after dobutamine at the late CPB separation phase (figs. 2 and 3).

When analyzed for individual baseline RWM score, dobutamine echocardiography remained a highly significant predictor for early and late functional changes ($P < 0.0001$). Baseline score was not a significant predictor of response to dobutamine and did not affect the relationship between response and improvement at early or late phases after CABG. For baseline RWM score 2, for example, the ORs for early and late function changes were 17.3 and 36.5, respectively. The probability of having an improved score at 5 min after CPB if there was an improvement after low-dose dobutamine was 0.87 (positive predictive value). The probability of having the same or worse score at 5 min after CPB if there was no improvement after dobutamine was 0.72 negative predictive value). The positive predictive value and negative predictive value for regional function changes 30 min after the administration of protamine were 0.94 and 0.69, respectively. For baseline RWM score 3, the ORs for early and late function changes were 18.9 and 36.2, respectively, with a positive predictive value of 0.91 and a negative predictive value of 0.65 for early change. At 30 min after protamine infusion, the positive predictive value was 0.94 and the negative predictive value was 0.70 for late functional changes. When baseline scores 4 and 5 were pooled and evaluated, the positive predictive values for early and late intervals were 0.83 and 0.91, respectively.

Of 2,240 segments independently analyzed, there were 245 disagreements (11%) after one scoring. One segment was unreadable by observer 1 but scored by observer 2; 49 segments were unreadable by observer 2 but scored by observer 1. Both observers agreed that 31 segments (1.5%) were unreadable. Agreement between the two observers after the first scoring was substantial for all evaluations (κ statistic range, 0.74–0.81; $P < 0.0001$) at baseline (86%), after low-dose dobutamine

Table 2. The Positive Predictive Value and Negative Predictive Value for Regional Changes after Low–Dose Dobutamine in Diabetic Patients Compared with Nondiabetic Patients

	Early		Late		Segments Analyzed (n)
	Positive Predictive Value	Negative Predictive Value	Positive Predictive Value	Negative Predictive Value	
Diabetes	0.86	0.54	0.96	0.61	155
No diabetes	0.92	0.81	0.91	0.77	134

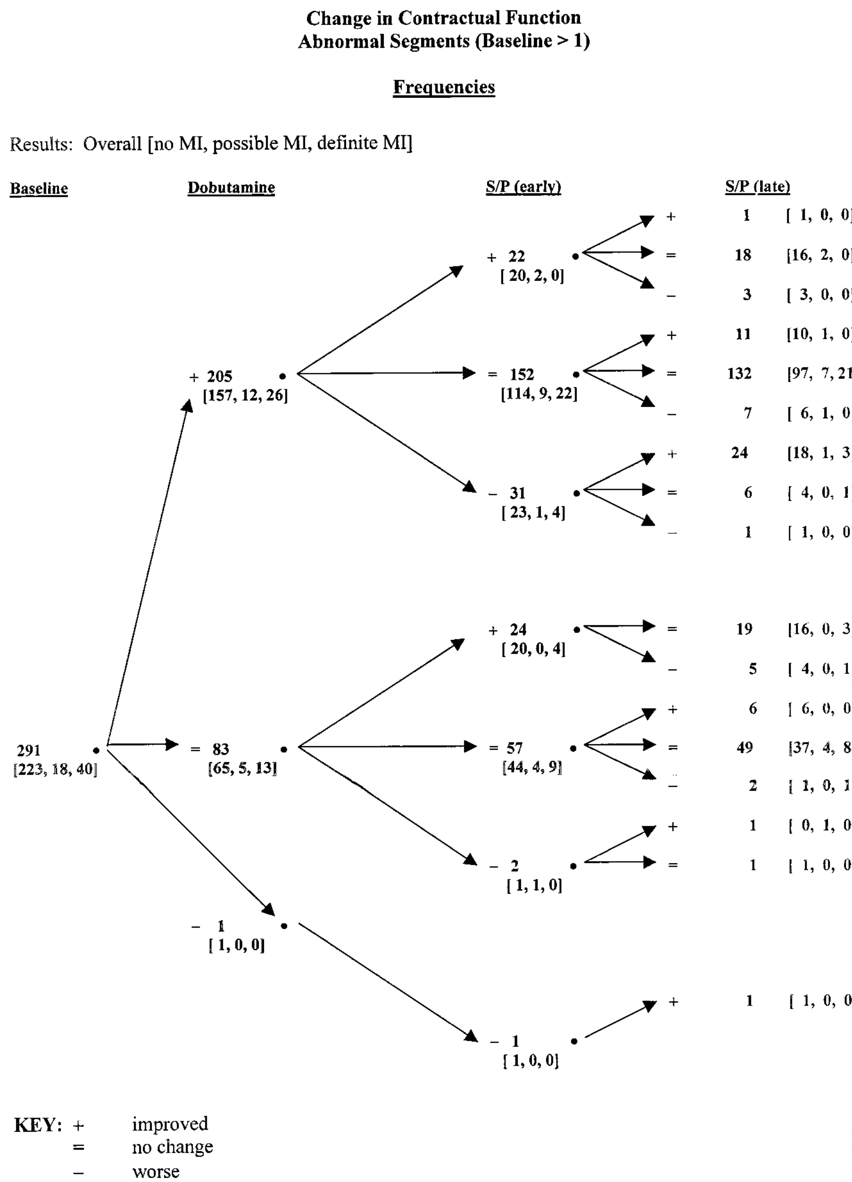

Fig. 2. Change in function of abnormal segments (baseline > 1). Early refers to status after early separation from cardiopulmonary bypass. Late refers to status 30 min after administration of protamine. Numbers in brackets refer to key at top (from left to right: no MI, possible MI, definite MI). Top arrows refer to improvement, middle arrows refer to change, and bottom arrows refer to worsening.

(92%), after CPB (88%), and after protamine (89%). For the 245 segments on which the observers disagreed, the scores almost always differed by one point (97%) and never differed by more than two. For 71% of readable segments, the observers agreed at all four time points and disagreed at only one of the four time points for 17% of the segments. Disagreement at more than one time point occurred for 12% of the segments (7.7% at two time points, 2.6% at three time points, and 1.4% at all four time points). When scores differed at one time point, the difference occurred most frequently at baseline (40 of 87) and least frequently at low-dose dobutamine (5 of 87). Otherwise, disagreements were evenly distributed among the time points. There was an 8.5% rate of continued disagreement between the reviewers for all segments analyzed (6.8% for readable segments) after repeated evaluation. Among the initial discordant segments, one observer modified his initial score 26% of the time and the other 49% of the time.

Discussion

Evidence supports the premise that CABG surgery contributes to improved regional and global left ventricular

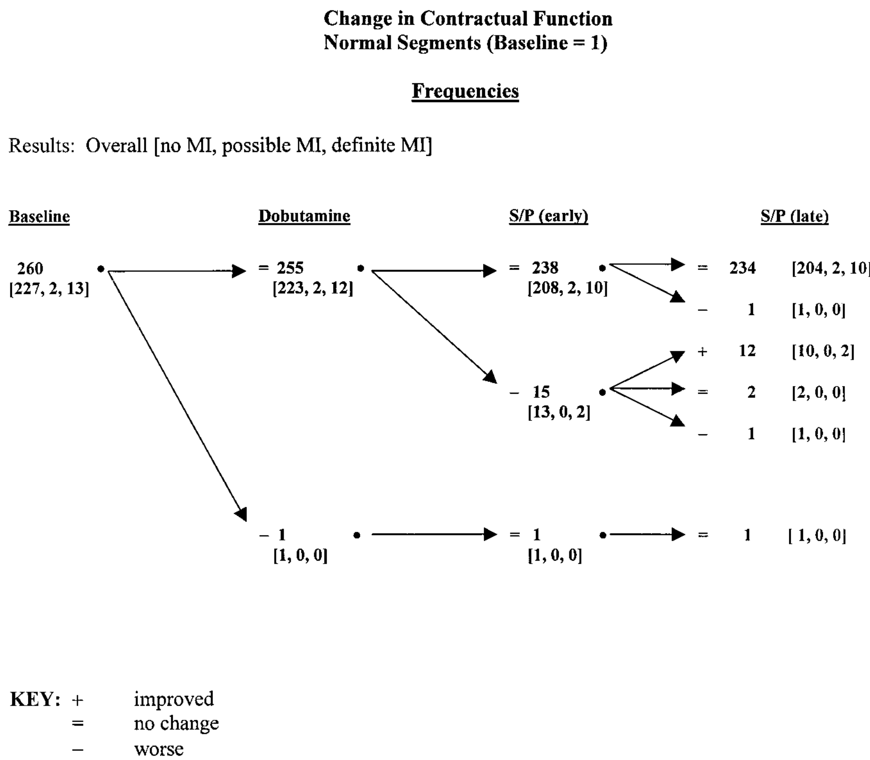

Fig. 3. Change in function of normal segments (baseline = 1). Early refers to status after early separation from cardiopulmonary bypass. Late refers to status 30 min after administration of protamine. Numbers in brackets refer to key at top (from left to right: no MI, possible MI, definite MI). Top arrows refer to no change and bottom arrows refer to worsening.

function in patients with left ventricular dysfunction with or without angina and infarction.[17,18] However, few studies provide evidence to demonstrate the adequacy of complete revascularization intraoperatively.[19] Preoperative dobutamine stress echocardiography offers a method before surgery to identify patients who should benefit from interventional medical or surgical myocardial revascularization procedures.[20–23] Monitoring global indices of left ventricular performance after CABG may not reveal isolated regional dysfunction. Consequently, residual left ventricular compromise after coronary revascularization may be limited to a discrete region of the left ventricle with otherwise normal cardiac output or ejection fraction. We used intraoperative transesophageal echocardiography and low-dose dobutamine before revascularization to establish an intraoperative standard for expected changes in regional function after surgical revascularization.

Dobutamine stress echocardiography has been credited with being a safe and reliable means of diagnosing coronary artery disease and predicting improvement of dysfunctional myocardium preoperatively.[24] Low-dose dobutamine may elicit an improved contractile response from myocardial segments that are abnormal at rest because of hibernating or stunned myocardium (acute ischemia–reperfusion). For the purposes of this study, we defined hibernating segments (chronic ischemia) to be abnormal at rest (after induction of anesthesia and before dobutamine infusion) and improved after dobutamine infusion unless there was history of acute ischemia–reperfusion that contributed to baseline dysfunction with improved contractile reserve after dobutamine (stunning). If abnormal segments did not improve after low-dose dobutamine, they were considered infarcted. Segments that were normal before dobutamine infusion were expected to remain normal after CABG. In this way, regions with contractile reserve were determined intraoperatively.

We demonstrated that the ORs for early and late improvement in myocardial function were 20.7 and 34.6, respectively, when improvement was observed with dobutamine. In other words, if patients had improved RWM scores after intraoperative low-dose dobutamine (before CABG), then the chance of having improved RWM scores was 20.7-fold higher at 5 min after separation from CPB and 34.6-fold higher at 30 min after protamine than without improved RWM scores after dobutamine. A history of myocardial infarction in a specific segment, preoperative ejection fraction, and β blocker use were covariates that did not influence positive predictive value in each segment. Although improvement in regional contractile function with dobutamine was strongly predictive of improvement at early and late phases compared with baseline, lack of improvement was less predictive, especially for patients with diabetes.

At the completion of CABG, new or abnormal RWM that was not expected needs to be recognized and identified as either inadequately revascularized or as a manifestation of acute reversible ischemic changes (stunning). Stunning occurs in approximately 8–10% of myocardial segments after CABG surgery.[25]

Information to guide surgical decisions, such as which myocardial segment should be revascularized with which conduits (arterial, vein, or not at all), reexploration of a graft conduit, reevaluation of graft conduits subtending a region devoid of adequate blood flow, or providing temporary exogenous circulatory support to revascularization until expected recovery, depends on an understanding of the functional recovery of myocardial segments at risk. These perioperative decisions become all the more important in a patient with severely compromised preoperative left ventricular dysfunction. Indeed, coronary revascularization has the potential to benefit most the patients with the greatest degree of myocardial dysfunction with evidence of viability.[26–30] The challenge in these patients is to identify the viable regions expected to improve and to determine whether revascularization has fulfilled the predictions for improvement in regional myocardial function.

The incidence and degree of functional recovery after coronary revascularization depends on a number of factors, including the severity of global left ventricular dysfunction preoperatively, myocardial protection techniques, the presence of perioperative myocardial infarction, and the adequacy of repair. Data suggest that recovery of function after surgery varies widely, occurring in 25–80% of dysfunctional segments.[31] Revascularization of viable but dysfunctional myocardium perfused by markedly obstructed vessels can reduce the threat to the myocardium and improve left ventricular function.[31] Discrimination between viable yet poorly contractile myocardium and nonviable tissue is important. With angiographic evaluation of regional contraction and coronary artery anatomy, one cannot distinguish between viable and irreversibly damaged tissue. Furthermore, it has been demonstrated that up to 50% of patients with a previous infarction may have areas of hibernating tissue mixed with areas of scar tissue, even in the presence of Q waves on the electrocardiogram.[32] Hibernating myocardium can be discovered with imaging techniques that detect the presence of functional reserve or the persistence of metabolic activity within dysfunction regions. Nuclear techniques that rely on demonstration of membrane integrity or residual metabolic activity are not practical for intraoperative use. Among the other methods to identify viable myocardium (*e.g.*, single proton emission computer tomography, magnetic resonance imaging, and contrast echocardiography), only contrast echocardiography, an imaging technique to assess microvascular integrity, seems feasible for intraoperative assessment. A limitation of this study was the lack of a method to establish adequate flow intraoperatively.

We have shown that intraoperative low-dose dobutamine echocardiography can be used to reliably predict functional changes after CABG surgery. Further research is needed to anticipate abnormal function after revascularization even when evaluation of myocardial functional reserve before CABG seems to predict normal function. The data in this study support previous reports that this subset represents approximately 8–10% of regional myocardial abnormalities detected at the completion of CABG surgery.

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