

Relationship of Regional Wall Motion Abnormalities to Hemodynamic Indices of Myocardial Oxygen Supply and Demand in Patients Undergoing CABG Surgery

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To investigate the hemodynamic correlates of perioperative regional wall motion abnormalities (RWMA), we measured wall motion continuously *via* transesophageal echocardiography (TEE), and related RWMA to continuously measured hemodynamic indices of myocardial oxygen supply and demand (heart rate [HR] and systemic and pulmonary arterial blood pressures). Fifty patients undergoing coronary artery bypass graft (CABG) surgery were studied throughout the prebypass, postbypass, and intensive care unit (ICU) periods. Only 28% of TEE episodes (RWMA suggestive of ischemia) were preceded by acute changes in any hemodynamic parameter. Specifically, 7% of TEE episodes were preceded by increases in HR (20% deviation from control), 14% by increases in systolic blood pressure (SBP), 13% by decreases in diastolic blood pressure (DBP), and 9% by increases in pulmonary artery diastolic pressure (PAD). Twelve per cent of TEE episodes were associated with increases in rate-pressure product (RPP) to >12,000, and 27% were associated with decreases in mean arterial pressure (MAP)/HR to <1 at the onset of TEE episodes. Comparison among periods revealed that postbypass TEE episodes were more frequently associated with either increases in demand or decreases in supply than were prebypass episodes (53% *vs.* 25%, $P < 0.05$). ECG ischemic episodes also were infrequently (30%) associated with acute changes in HR, SBP, DBP,

or PAD. We conclude that perioperative TEE episodes are infrequently triggered by changes in hemodynamics, suggesting that a primary decrease in myocardial oxygen supply may be an important mechanism for most perioperative RWMA. In addition, neither pulmonary artery catheter pressure measurements nor specialized indices (RPP and MAP/HR) appear to be useful in predicting TEE episodes. (Key words: Heart: coronary artery disease, myocardial ischemia, etiology, supply and demand. Monitoring: hemodynamics, pulmonary artery catheter, transesophageal echocardiography, blood pressure, pulse rate, Holter electrocardiography. Surgery: coronary artery bypass graft. Anesthesia: cardiac.)

REGIONAL WALL MOTION abnormalities (RWMA) are sensitive and early markers of myocardial ischemia, as demonstrated by a number of experimental and clinical studies in animals and humans.^{1-10,¶} We previously reported that RWMA detected by transesophageal echocardiography (TEE) are common in patients undergoing coronary artery bypass graft (CABG) surgery,¹⁰ and that postbypass RWMA appear to be predictive of postoperative morbidity and mortality.^{10,11} Despite the apparent importance of perioperative RWMA, few studies have investigated their etiology.¹² Since an imbalance between myocardial oxygen supply and demand may result in RWMA, understanding the relationship between RWMA and the hemodynamic indices of supply and demand is of fundamental importance. Only by defining this relationship can appropriate therapies be chosen to lower the incidence of intraoperative RWMA and subsequent associated adverse outcomes.

To investigate the relationship between hemodynamic changes and RWMA, we continuously monitored both RWMA and hemodynamic indices of supply and demand throughout the perioperative period. Our specific aims were: 1) to relate RWMA to indices of myocardial oxygen demand (increases in heart rate [HR], increases in systolic blood pressure [SBP], and increases in pulmonary artery diastolic pressure [PAD]) and to indices of myocardial

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¶ The term "ischemia" is used to indicate those TEE RWMA or ECG ST changes suggestive of ischemia. We recognize that without an absolute reference standard, not all such RWMA or ST-segment abnormalities are necessarily indicative of myocardial ischemia.

oxygen supply (increases in HR, decreases in diastolic blood pressure [DBP], and increases in PAD); and 2) to assess the value of the specialized indices: rate-pressure product (RPP) and mean arterial pressure (MAP)/HR in predicting RWMA.

Materials and Methods

PATIENT SELECTION

Fifty consecutive patients (49 men and 1 woman, 42–78 yr old) scheduled for elective CABG surgery because of unstable angina (25 patients) or stable progressive angina (25 patients) were studied at the San Francisco Veterans Administration Medical Center between August 1987 and March 1988. We obtained approval from our Committee on Human Research and written informed consent from each patient. The demographic and clinical data obtained for each patient included a history of prior myocardial infarction, previous CABG surgery or angioplasty, hypertension, diabetes mellitus, unstable angina, and preoperative medications. Preoperative ejection fraction was determined by ventriculography, and the number of significant coronary arterial stenoses noted. Significant stenosis is defined as $\geq 70\%$ luminal stenosis of the left anterior descending, left circumflex, or right coronary artery and $\geq 50\%$ diameter stenosis of the left main coronary artery. These 50 patients were the subjects of our previous study examining the prognostic significance of RWMA.¹⁰

ANESTHETIC MANAGEMENT

Patients received diazepam and morphine sulfate as preanesthetic medication, and all cardiac medications were continued until the time of operation. Anesthesia consisted of one of the following: high-dose sufentanil ($n = 31$), fentanyl ($n = 5$), isoflurane supplemented with fentanyl ($n = 12$), or halothane ($n = 2$). Routine clinical monitors included 7-lead electrocardiography (ECG) and radial artery and pulmonary artery catheters. The administration of vasodilators, vasopressors, and inotropic drugs was measured but was not controlled. All patients received 100% inspired O_2 to maintain $Pa_{O_2} > 70$ mmHg, and ventilation was controlled to maintain Pa_{CO_2} between 35 and 45 mmHg. The lungs of all patients were ventilated with a tidal volume of 10–15 ml/kg, and mean peak inspiratory pressure was 20 cmH₂O (range 12–30 cmH₂O). All clinicians providing direct patient care were blinded to the research information obtained from the echocardiographic and specialized ECG monitoring.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Immediately after tracheal intubation, a gastroscope tipped with either a 3.5-MHz (Diasonics Inc., Milpitas, CA) or a 5-MHz phased-array transducer (General Electric

Co., Milwaukee, WI) was introduced into the esophagus. The transducer was positioned and maintained at the level of the midpapillary muscles to obtain a short-axis view of the left ventricle. Echocardiographic data were recorded continuously onto videotapes during the 1) prebypass period, *i.e.*, from completion of tracheal intubation to the onset of cardiopulmonary bypass; 2) postbypass period, *i.e.*, from completion of the last proximal graft insertion to skin closure; and 3) ICU period: 5 min/h for the first 4 h.

The real-time videotape was edited to obtain samples for analysis, and yielded an average of 32 samples (range 19–45) per patient. Echocardiographic samples of 60-s duration were obtained every 15 min throughout the intraoperative recording. Additionally, samples were obtained at other prespecified times to detect whether anesthetic or surgically imposed stresses had any immediate effect on regional wall motion. During the prebypass period, samples were obtained immediately after tracheal intubation, as well as at 4 min before and 1 and 6 min after each of the following surgical events: skin incision, sternotomy, pericardiotomy, and aortic and right atrial cannulation. Data obtained after completion of the last proximal graft insertion (*i.e.*, release of the aortic side-biting clamp) were edited as follows: samples were obtained every 5 min until 1 h postbypass and then every 15 min until skin closure. Additional samples were obtained 1 and 6 min after sternal closure. In the ICU, samples were obtained at the time of the patient's arrival and after 1, 2, and 3 h. To blind the echocardiographic readers, the temporal sequence of the samples was scrambled before analysis. The samples were then rearranged in chronologic order after scoring, and TEE episodes were determined. Each patient's best prebypass wall motion score was used as his or her baseline.

The short-axis, cross-sectional image was divided into four segments with the use of the papillary muscles as guides. This floating-reference system compensated for translational and rotational movements of the heart. A segment was considered suitable for wall motion analysis if 70% of its entire endocardial outline was visible continuously during systole and diastole. All samples were analyzed visually by two investigators by consensus; these investigators were blinded to patient identity, clinical outcome, and time of sampling. The wall motion of each of the four segments was graded as follows: 0 = normal; 1 = mild hypokinesis; 2 = severe hypokinesis with myocardial thickening; 3 = akinesis; and 4 = dyskinesis. Myocardial thickening was estimated by visual inspection in real time and slow motion. A "TEE episode" suggestive of ischemia was defined by regional wall motion worsening of two or more grades and lasting ≥ 1 min.

To determine the effects of interobserver variability over time, 320 scrambled samples from ten randomly chosen patients were reread by the same two observers,

by consensus, approximately 6 months after the first reading. There was 94% agreement in correctly identifying an ischemic episode. Inter- and intraobserver variability during the study was determined by having both observers independently analyze a preselected tape of 50 samples twice. A discrepancy between observations was defined by a difference of two or more grades in scoring a segment. The degree of interobserver variability was 3%. Intraobserver variability was 2% (for both observers).

ELECTROCARDIOGRAPHY

ECG monitoring was performed with a two-channel AM Holter ECG recorder (series 8500, Marquette Electronics) from the time of anesthetic induction to the removal of the echocardiographic probe in the ICU. The frequency response met the American Heart Association specification for ST changes (the cut-off limit is 0.05 Hz for low frequency and 80 Hz for high frequency). Two bipolar leads, CC5 and modified CM5, were used. Each complete ECG recording on Holter tape was scanned visually with an ECG analysis system (series 8000, Marquette). All abnormal QRS complexes (*e.g.*, ventricular ectopic beats and conduction abnormalities) were excluded. A continuous two-lead ST-segment trend then was generated for the entire tape. The baseline ST-segment level was defined as the average ST segment during a stable period (usually 1 h) preceding each episode. All possible ischemic episodes were reviewed and verified by two investigators who were blinded to patient's identity and outcome. An ECG ischemic episode was defined as reversible ST depression of ≥ 0.1 mV from baseline at J + 60 ms, or ST elevation of > 0.2 mV at the J point and lasting for at least 1 min. During tachycardia, when J + 60 ms fell within the T wave, the time after the J point was shortened to a minimum of J + 40 ms.

HEMODYNAMICS

Intraoperatively, SBP and DBP were monitored continuously in all 50 patients with radial artery catheters. HRs were derived from the ECG tracings. Pulmonary artery systolic and diastolic pressures were monitored continuously in 47 patients (3 patients did not have interpretable tracings). In the ICU, hemodynamic data (HR, SBP, DBP, and pulmonary artery pressures) were collected prior to and during the TEE recordings. All hemodynamic data were recorded continuously onto hard copy at 1 mm/s with a four-channel strip-chart recorder (4-Inch Direct Digital Writer, Marquette) linked to the hemodynamic monitor (Marquette 7010) throughout the intraoperative period and intermittently in the ICU period. Hemodynamic data were averaged every 90 s and printed onto hard copy. The frequency responses for the clinical ECG monitor are 0.05–120 Hz and those for the pressure transducers are 0–42 Hz. The zero reference

point was located 5 cm posterior to the sternal angle in a direction perpendicular to the frontal plane of the chest. The time clocks on the TEE, Holter monitor, and hemodynamic recorder were synchronized prior to anesthetic induction.

Preoperative baseline hemodynamic values for HR, SBP, and DBP for each patient were determined by averaging the last five preoperative values obtained for each variable. Measurements were obtained during the 48 h preoperative period while the patients were on maximal medical therapy. The baseline for PAD was determined by averaging the first five preinduction values.

The hemodynamic data were analyzed as follows: 1) data on the hard copy were reviewed to ensure that artifacts (such as erroneous values resulting from blood drawing or flushing of catheters) were excluded from analysis; 2) HR, SBP, DBP, and PAD were sampled from the hard copy data every 90 s, and the data were entered into a computer spreadsheet (Statview 512+, Brainpower, Calabassas, CA); 3) the frequency distributions for HR, SBP, DBP, and PAD were determined for the entire prebypass and postbypass periods for each patient; and 4) hemodynamic episodes were identified, with significant episodes defined by a $> 20\%$ increase (HR, SBP, and PAD) or decrease (DBP) from preoperative baseline lasting 60 s or longer.

To determine whether TEE or ECG ischemic episodes were preceded by acute hemodynamic changes, we compared the hemodynamic values at the onset of each type of ischemic episode with values measured at 5 and 10 min before onset. Since hemodynamic aberrations may occur gradually (over minutes to hours), ischemic episodes also may be precipitated by chronic rather than acute hemodynamic changes. We therefore compared the preoperative value with the hemodynamic value at onset as well.

OPERATIVE TECHNIQUE

Cardiopulmonary bypass was performed with the use of a bubble oxygenator using hemodilution and moderate systemic hypothermia (26–28° C). Multiple-dose cold blood (8° C, hematocrit 20–25%) with potassium cardioplegia (20 mEq/l) and topical saline/ice slush were used for myocardial protection during cardiopulmonary bypass. Distal anastomoses were performed during continuous aortic cross-clamping and were followed by proximal vein grafting during partial aortic occlusion. Forty-eight patients received vein grafts; 44 patients received internal mammary artery grafts to either the left anterior descending or the first diagonal coronary artery. The pericardium was left open in all patients.

The quality of the bypass grafts was assessed by surgeons who were unaware of the echocardiographic and hemodynamic findings. The grafts were graded qualitatively as poor, fair, very good, and excellent. All grafts were found to be fair to excellent.

STATISTICAL METHODS

Chi-squared analysis with continuity correction or Fisher's Exact Test were applied to categorical data. Student's *t* test was used to test the difference between the means in the two groups. Differences in HR and BP for the prebypass, postbypass, and ICU periods were assessed by one-way analysis of variance (ANOVA) using repeated measures. A *P* value of <0.05 (two-sided) was considered statistically significant.

Results

RELATIONSHIP OF TEE EPISODES TO ACUTE CHANGES IN HEMODYNAMICS

Fifty patients were monitored for a total of 197 h with continuous TEE, ECG, and hemodynamic measurements. A total of 56 TEE episodes were detected in 22 patients: 10 patients had 16 episodes prebypass, 18 patients had 28 episodes postbypass, and 12 patients had 12 episodes (1 each) in the ICU. Two patients were not followed in the ICU: one could not be separated from bypass and died intraoperatively; the other was on bypass for 4 h and subsequently required intraaortic balloon counterpulsation for ventricular failure.

For each episode, the SBP and HR at episode onset was compared to the baseline value (10 min before) (figs. 1A–C): no consistent directional change was observed for SBP or HR during any period. Similarly, no consistent directional change was found for PAD. The baselines measured at 5 and 10 min before the onset of the episodes were similar.

The distribution of hemodynamics at episode onset (figs. 2A–D) revealed that the mean postbypass and ICU HR values at onset were higher than prebypass values ($P < 0.05$) and that the mean postbypass SBP and DBP values at onset were lower than prebypass values ($P < 0.05$), whereas the mean PAD values were similar for the three periods ($P = \text{NS}$) (table 1). The overall relationship to hemodynamic abnormalities (fig. 3) demonstrated that 72% of TEE episodes occurred without acute changes in HR, SBP, DBP, or PAD. The individual period results (fig. 4) also revealed a weak relationship between TEE episodes and either decreases in myocardial oxygen supply indices (increases in HR, decreases in DBP, or increases in PAD), or increases in demand indices (increases in HR, SBP, PAD). A greater number of postbypass than prebypass TEE episodes were hemodynamically related (supply or demand) ($P = 0.03$). There were more hemodynamically related TEE episodes in the ICU than there were prebypass, but this difference was not significant ($P = 0.18$). However, nearly 50% of postbypass episodes and most ICU episodes were unrelated to any change in hemodynamics.

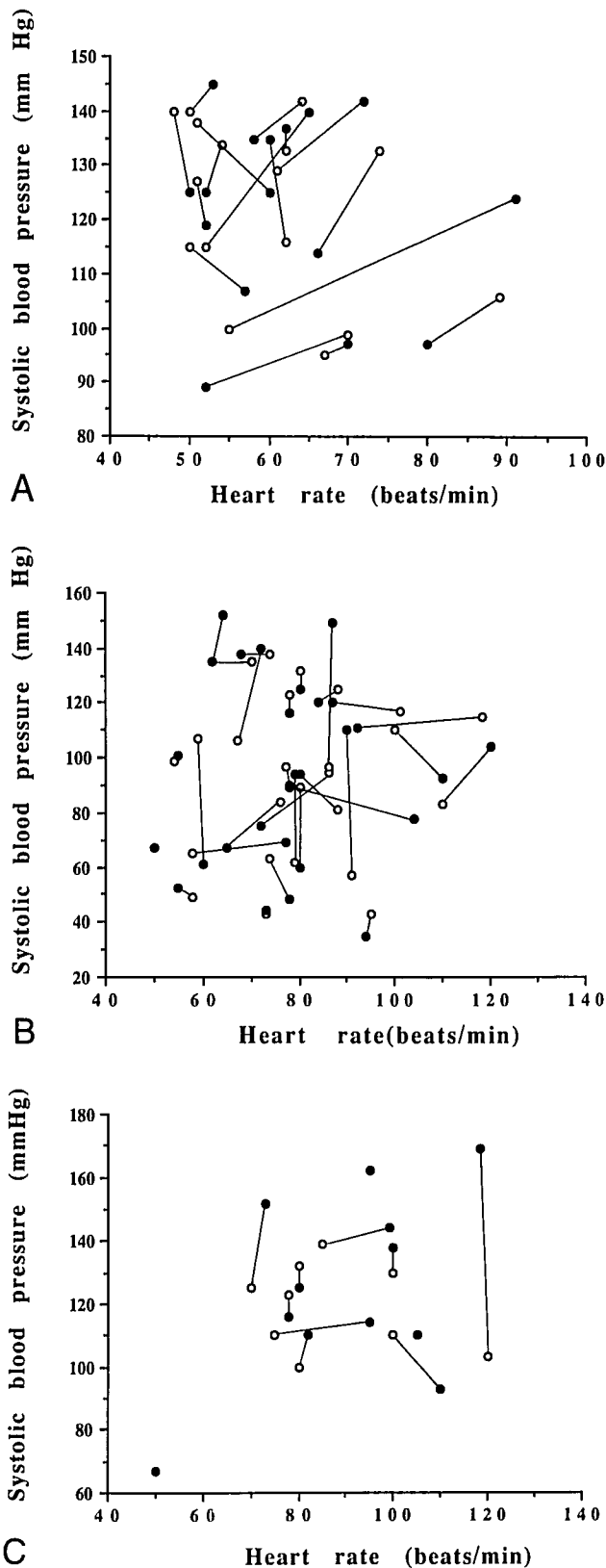


FIG. 1. SBP and HR at the onset (filled circles) of TEE episodes as compared with the control values (open circles) measured 10 min before, for the prebypass (A), postbypass (B), and ICU (C) periods.

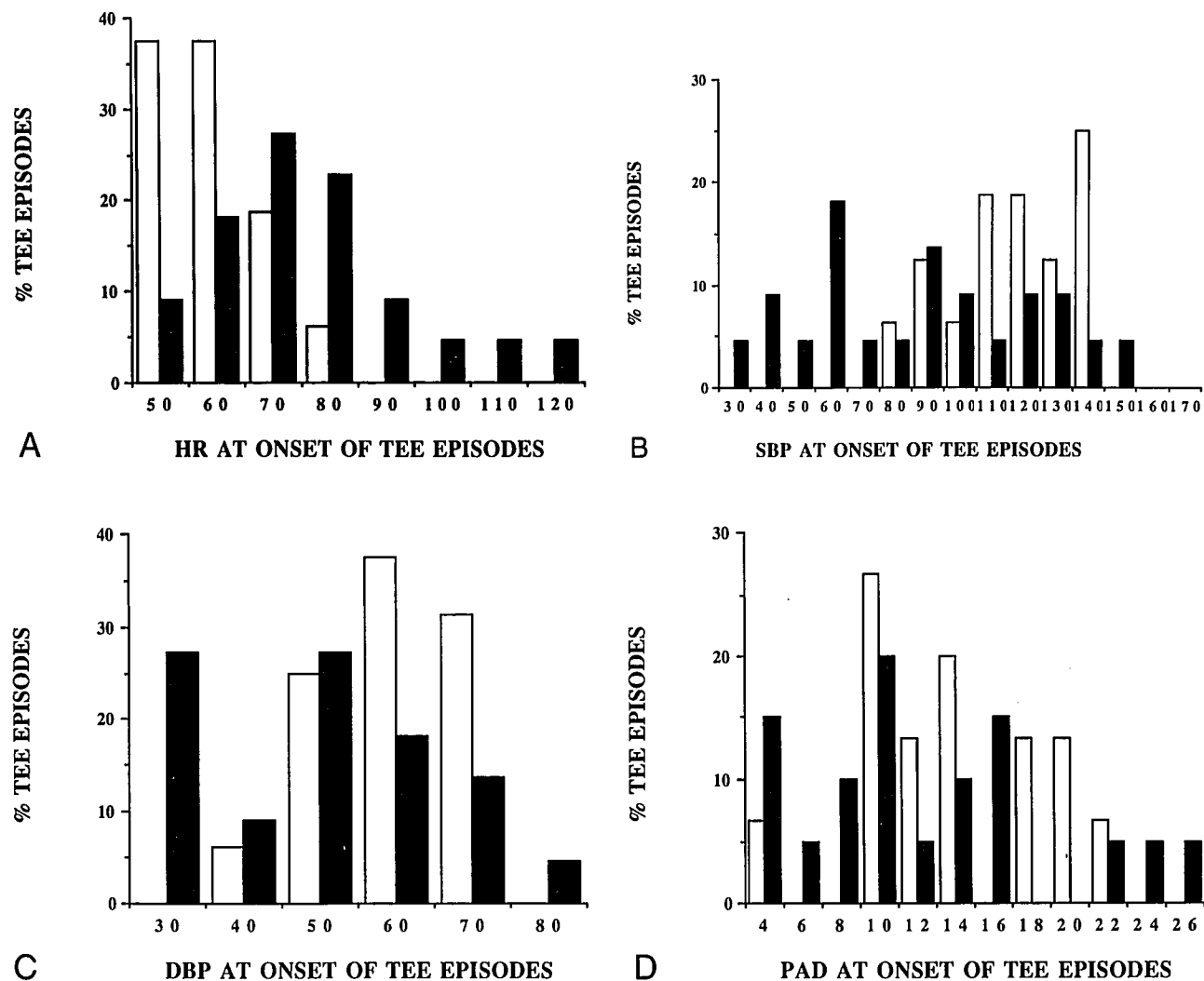


FIG. 2. (A–D) The frequency distributions of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulmonary artery diastolic pressure (PAD) at the onset of the TEE episodes are shown for the prebypass (open squares) and postbypass (filled squares) periods.

RELATIONSHIP OF TEE EPISODES TO SPECIALIZED HEMODYNAMIC INDICES

The relationship between RWMA and acute changes in RPP or MAP/HR (figs. 5A–C, 6A–C) demonstrated that 48% of TEE episodes (56% prebypass, 43% postbypass, and 50% ICU) were associated with an increase in RPP (mean increase 28%, range 1–105%). Fifty per cent of TEE episodes (56% prebypass, 43% postbypass, and 58% ICU) were associated with a decrease in the MAP/HR index (mean decrease 14%, range 1–14%). A RPP value of >12,000 was obtained for only 12% of all TEE episodes, and a MAP/HR <1 for only 27%. Other RPP thresholds (14,000–20,000) and MAP/HR thresholds (1.2–2.0) also demonstrated weak relationships with TEE episodes (table 2).

RELATIONSHIP OF HEMODYNAMIC EPISODES TO TEE FINDINGS

The distributions of HR, SBP, DBP, and PAD for the prebypass and postbypass periods for the 50 patients were examined. The distributions for these variables were not available during the ICU period because ICU data were recorded hourly. The mean HR (\pm SD) postbypass (80 ± 12 beats per min) was higher than that prebypass (60 ± 17 beats per min, $P < 0.001$); the mean SBP postbypass (106 ± 11 mmHg) was lower than that prebypass (121 ± 12 mmHg, $P < 0.001$); and the mean DBP postbypass (60 ± 10 mmHg) lower than that prebypass (63 ± 6 mmHg, $P < 0.01$). Mean PAD for these two periods (14 ± 4 mmHg) did not differ between periods ($P = \text{NS}$).

Hemodynamic episodes were defined as >20% increase

TABLE 1. Hemodynamics at the Onset of RWMA

	Prebypass	Postbypass	ICU
HR (beats per min)	63 ± 3	78 ± 3*	98 ± 5*
SBP (mmHg)	121 ± 5	95 ± 6*	141 ± 9
DBP (mmHg)	63 ± 3	55 ± 3*	76 ± 3
PAD (mmHg)	14 ± 1	13 ± 1	13 ± 1

RWMA = regional wall motion abnormalities; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; PAD = pulmonary artery diastolic pressure; ICU = intensive care unit. Values are mean ± SE.

* Significantly different from prebypass, $P < 0.05$.

in HR, SBP, or PAD, and >20% decrease in DBP from preoperative values. The relationship of hemodynamic episodes to TEE episodes is given in table 3. For example, 9 of 37 (24%) HR episodes were associated with TEE episodes in the prebypass period, versus 68 of 118 (58%) during postbypass ($P < 0.001$). Most (67–100%) prebypass hemodynamic episodes were not associated with RWMA; postbypass increases in SBP and PAD also were not associated with RWMA. However, 58% of postbypass HR episodes (tachycardia) and 82% of DBP episodes (hypotension) were associated with RWMA.

RELATIONSHIP OF ECG ISCHEMIC EPISODES TO ACUTE CHANGES IN HEMODYNAMICS

A total of 20 ECG ischemic episodes were detected in 19 patients. The incidence was 15% prebypass, 55% postbypass, and 30% ICU. No episode was associated with an

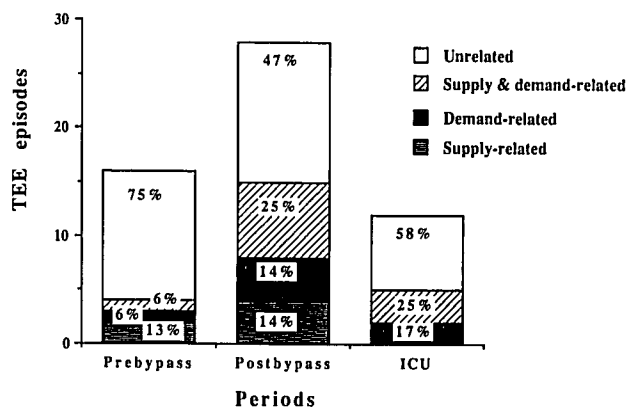


FIG. 4. Distribution of TEE episodes in the prebypass, postbypass, and ICU periods and their association with hemodynamic indices of supply and demand.

increase in HR (>20% from control, measured either 5 or 10 min before onset of an ECG episode); 15% were associated with an increase in SBP; 10% were associated with a decrease in DBP; and 10% were associated with an increase in PAD. Overall, 30% of ECG ischemic episodes were associated with acute changes in HR, SBP, DBP, or PAD. Of the 20 ischemic episodes, 18 had interpretable TEE recordings (2 did not have simultaneous TEE recordings because the ECG episodes occurred early in the ICU period when TEE recording was intermittent). Eight of the 18 episodes (44%) had corresponding TEE ischemic changes. Of the 8 episodes with both TEE and ECG ischemic changes, 1 was associated with an increase in PAD, 1 with an increase in both SBP and PAD, and 1 with a decrease in DBP; 5 were not associated with any acute hemodynamic change.

RELATIONSHIP OF TEE AND ECG EPISODES TO HEMATOCRIT

Serial hematocrits were obtained in all 50 patients prebypass, immediately after protamine administration postbypass, and during the 1st h in the ICU. The mean (±SD) hematocrits for the three periods were $44 \pm 4\%$ prebypass, $26 \pm 3\%$ postbypass, and $28 \pm 4\%$ in the ICU. The mean decrease in postbypass hematocrit from prebypass values was similar for patients with and without postbypass TEE ischemic episodes (19 ± 4 vs. $16 \pm 6\%$, $P = 0.13$). Postbypass hematocrits did not differ for patients with and without postbypass TEE ischemic episodes (25 ± 3 vs. $26 \pm 3\%$, $P = 0.23$). Similarly, the mean decrease in postbypass hematocrit from prebypass values was the same for patients with and without postbypass ECG ischemic episodes (18 ± 5 vs. $17 \pm 2\%$, $P = 0.54$), and postbypass hematocrits did not differ for patients with and without postbypass ECG episodes (26 ± 3 vs. $25 \pm 2\%$, $P = 0.48$).

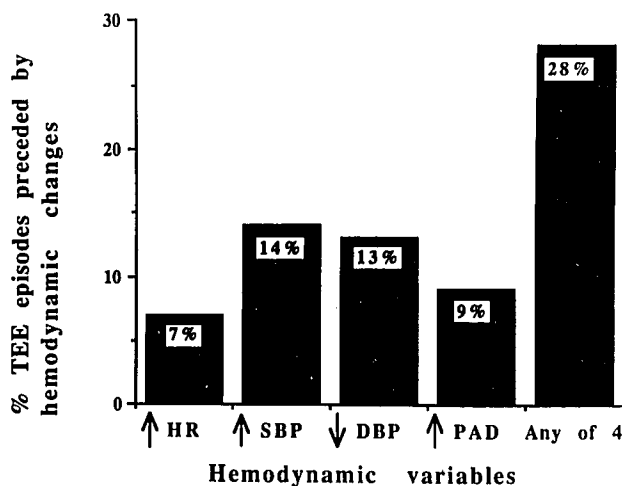


FIG. 3. TEE episodes associated with hemodynamic changes. Hemodynamics measured at 5 or 10 min before the onset of TEE episodes were used as controls. The percentage of TEE episodes associated with hemodynamic changes are those that were preceded by increases of >20% in heart rate, systolic blood pressure, and pulmonary artery diastolic pressure, or decreases of >20% in DBP from controls.

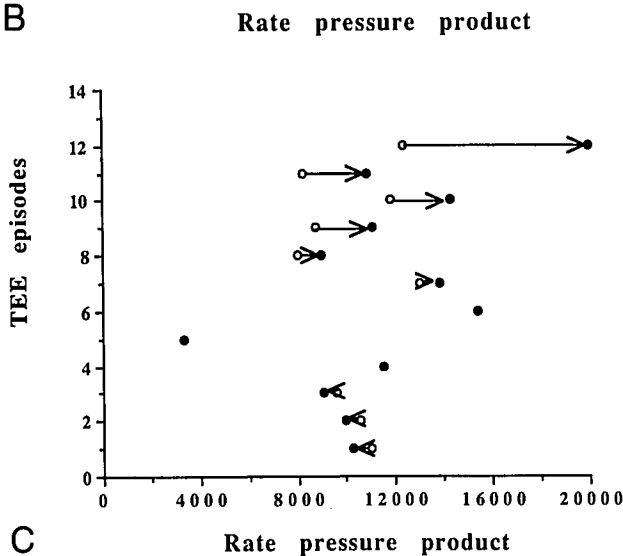
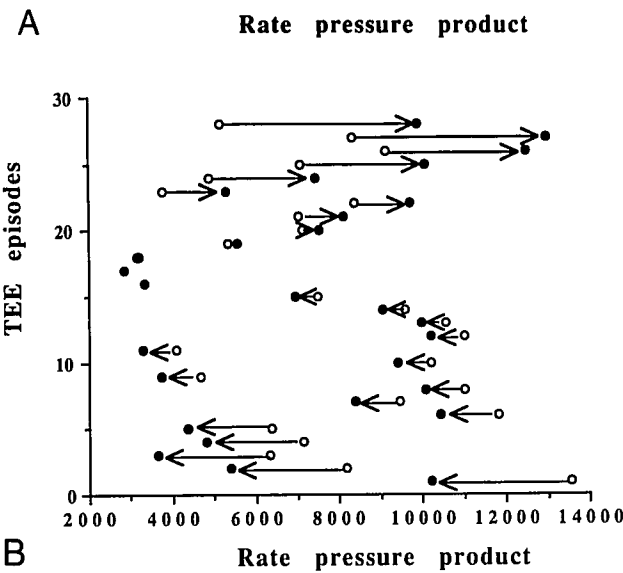
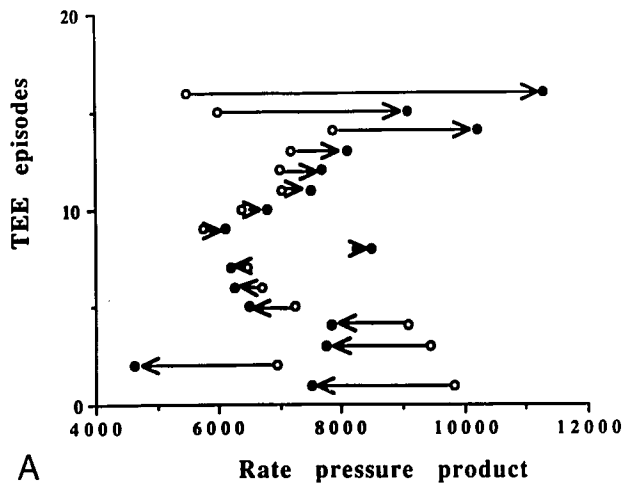


FIG. 5. The RPPs at the onset (filled circles) of TEE episodes are compared with the control (open circles) values measured 10 min before, for the prebypass (A), postbypass (B) and ICU (C) periods. The arrows indicate the directions of change.

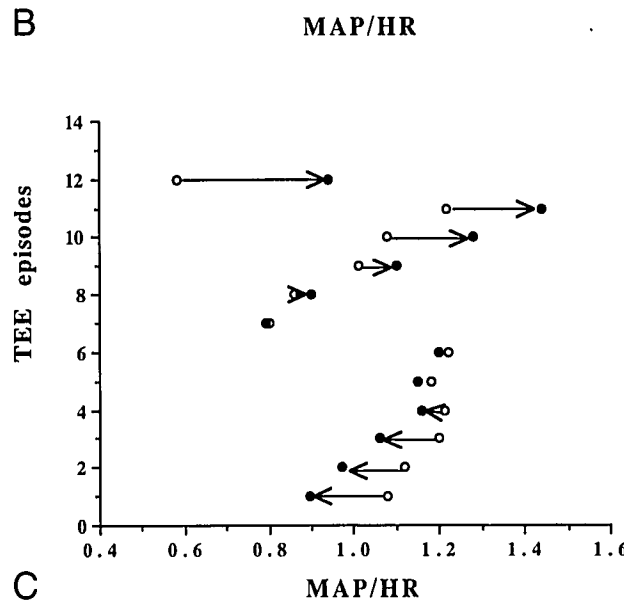
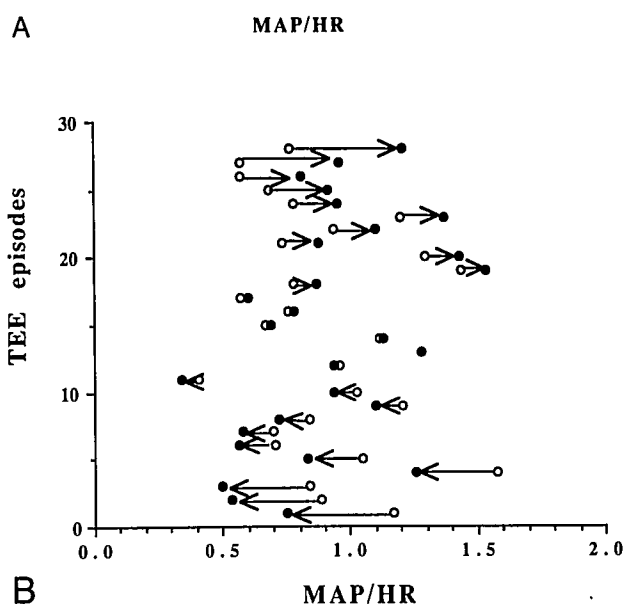
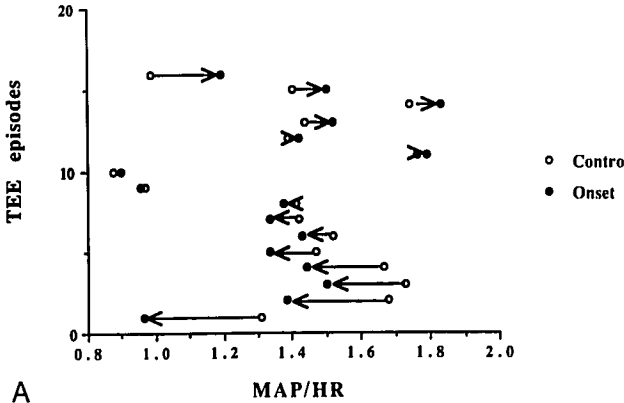


FIG. 6. The MAP/HR at the onset of TEE episodes as compared with the control values measured 10 min before, for the prebypass (A), postbypass (B), and ICU (C) periods. The arrows indicate the directions of change.

TABLE 2. Frequency Distribution of RPP and MAP/HR at Onset of TEE Episodes

	From (\geq)	To ($<$)	% of Episodes
RPP	2,000	4,000	12.5
	4,000	6,000	10.7
	6,000	8,000	23.2
	8,000	10,000	19.6
	10,000	12,000	23.2
	12,000	14,000	5.4
	14,000	16,000	3.6
	16,000	18,000	0.
MAP/HR	18,000	20,000	1.8
	0.2	0.4	1.8
	0.4	0.6	7.1
	0.6	0.8	10.7
	0.8	1.0	28.6
	1.0	1.2	14.3
	1.2	1.4	17.9
	1.4	1.6	16.1
	1.6	1.8	1.8
	1.8	2.0	1.8

Discussion

Using continuous assessment of hemodynamics and echocardiographic and ECG indices of ischemia, we found that: 1) TEE episodes were preceded infrequently by acute changes in hemodynamics (increases in HR, SBP, or PAD, or decreases in DBP); 2) RPP > 12,000 and MAP/HR < 1 were associated infrequently with TEE episodes; and 3) ECG episodes also were infrequently preceded by acute hemodynamic changes.

THE RELATIONSHIP BETWEEN ISCHEMIC EPISODES AND HR AND BP ABNORMALITIES

Acute changes in HR, blood pressure, or PAD preceded 28% of all TEE episodes and 30% of ECG ischemic episodes. Comparisons with previous echocardiographic studies are difficult because no previous study in patients

undergoing CABG surgery has assessed the relationship between RWMA and hemodynamic changes. Most studies of ECG ischemia indicate that a high percentage of these episodes are preceded by changes in HR or blood pressure.¹³⁻¹⁶ Using intermittent assessment of hemodynamics and ECG, Slogoff and Keats¹⁴⁻¹⁶ concluded that approximately 50% of ECG ischemic episodes were related temporally to HR and blood pressure abnormalities. In contrast, we found that only 25% of ECG ST changes and 23% of RWMA were associated with abnormalities in HR and blood pressure.

Additionally, our more rigorous definition of hemodynamic change allowed for the possibility and for the detection of even smaller changes in these parameters that might have precipitated RWMA. Slogoff and Keats defined hemodynamic abnormality as SBP ≥ 180 mmHg or ≤ 90 mmHg or HR ≥ 90 beats per min, and they found such abnormalities in 86% of their patients.¹⁵ It is surprising that despite stricter criteria, we found a lower incidence of hemodynamic change. This discrepancy can be explained by the difference in the degree of hemodynamic control. For example, only 25% of our prebypass HR values were >60 beats per min, and only 6% of our prebypass SBP values were >140 mmHg. The patients studied by Slogoff and Keats therefore had higher HRs and blood pressures during the prebypass period than did our patients. These marked hemodynamic fluctuations may have precipitated the higher incidence of prebypass ECG ischemia (28-43%) in their patients¹⁴⁻¹⁶ compared to the 7% in our current study. If intraoperative ischemic changes usually are not precipitated by hemodynamic changes except when they are substantial, then this hypothesis may in part explain why most of our ECG ischemic episodes tended to be unrelated to hemodynamic change. Furthermore, differences in patient characteristics (such as degree of coronary occlusion), in sensitivity of ECG monitors in detecting ischemia, and in the use of continuous as compared to intermittent ECG detection

TABLE 3. Relationship of Hemodynamic Episodes to TEE Episodes

	Prebypass Associated with RWMA		Postbypass Incidents Associated with RWMA		P
	Incidents	%	Incidents	%	
HR*	9/37	24	68/118	58	<0.001
SBP*	0/30		22/9	22	<0.05
DBP†	3/150	2	153/186	82	<0.001
PAD*	8/160	5	51/120	43	<0.001
RPP increase	1/3	33	3/23	13	NS
MAP/HR decrease	1/6	17	18/81	22	NS

HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; PAD = pulmonary artery diastolic pressure; RPP = rate-pressure product.

* Incident described as >20% increase.

† Incident described as >20% decrease.

P indicates a significant difference between pre- and postbypass values.

methods also may have contributed to the different findings.

CARDIAC FILLING PRESSURE

We found that only 9% of all TEE episodes and 10% of ECG episodes were preceded by an acute increase in PAD. These findings suggest that increases in PAD are insensitive markers for ischemia. Since pulmonary capillary wedge pressure cannot be measured continuously and be related to each ischemic episode, we studied PAD, which can be measured continuously. Furthermore, since PAD exceeds pulmonary capillary wedge pressure, it can be assumed that pulmonary capillary wedge pressure also did not increase before ischemic episodes. Thus, we can infer that pulmonary capillary wedge pressure also is an insensitive indicator of ischemia.

Our results contrast with earlier studies, which have suggested that pulmonary capillary wedge pressure or PAD may be early and sensitive markers of ischemia.^{17,18} However, the more recent findings of Häggmark *et al.*¹⁹ supported our findings. Häggmark *et al.* studied patients with coronary artery disease who were undergoing vascular surgery, and found that neither increased pulmonary capillary wedge pressure nor the presence of A-C or V waves greater than 5 mmHg above the mean reflected changes indicative of ischemia, *via* ECG, cardiokymography, or myocardial lactate extraction. Rahimtoola *et al.*²⁰ studied patients with acute myocardial infarction and found that increases in LV end-diastolic pressure were not reflected in mean diastolic pressure, left atrial pressure, or pulmonary capillary wedge pressure. Pulmonary capillary wedge pressure may not be a sensitive marker of ischemia because the end-atrial contraction (atrial systole) substantially contributes only to LV end-diastolic pressure but not to the other three pressures. Thus, compared to LV end-diastolic pressure, which has been shown to be an early and sensitive marker of ischemia,¹² the usefulness of pulmonary artery pressure monitoring for the detection of ischemia appears to be limited.

SPECIALIZED HEMODYNAMIC INDICES

We found that a RPP >12,000 did not predict TEE ischemic episodes. Even when the threshold was decreased to 10,000, only 34% of TEE episodes were related to it. Previous studies have both supported²¹⁻²⁵ and refuted²⁶⁻²⁸ the association between RPP and ECG ST changes indicative of ischemia. This variable may be unable to predict myocardial ischemia during anesthesia because HR and blood pressure may change in opposite directions (tachycardia and hypotension) intraoperatively.²⁹ Moreover, the RPP does not allow for variations

in ventricular dimensions, which will affect wall tension and modify myocardial oxygen requirements. In addition, anesthetics can influence the contractility of the heart (also not included in the index) and thereby alter myocardial oxygen consumption without changing HR or blood pressure.^{24,30}

In studies on dogs also, Buffington³¹ found that the RPP was not useful for predicting ischemia. After inducing severe stenosis, he found that ischemic dysfunction occurred only when MAP/HR < 1; that is, ischemia was absent when MAP/HR > 1. Although we found that approximately half of the TEE episodes were associated with decreases in MAP/HR, only 27% of these episodes occurred when MAP/HR < 1. The differences in results may be due to differences in study design. Data obtained from a canine model of coronary artery stenosis should be extrapolated to humans with caution. Anesthetized patients with coronary artery stenosis may have different collateral blood supply. In addition, differences in left ventricular function and volume, in anesthetic agents, and in methods of detecting ischemia exist. More importantly, if intraoperative myocardial ischemia results mainly from a primary decrease in myocardial oxygen supply, such as coronary vasospasm or thrombotic occlusion of a coronary artery, the resultant RWMA may occur independently of changes in arterial pressure and HR—a hypothesis supported by our findings.

Thus, because of the low sensitivity of RPP and MAP/HR measures in predicting ischemic changes, we question their routine use.

COMPARISON OF PRE- AND POSTBYPASS PERIODS

Comparison of RWMA to hemodynamic changes in the prebypass and postbypass periods revealed a noteworthy relationship. TEE episodes occurring in the postbypass period were associated more often with either increases in demand or decreases in supply. Although the myocardium is newly revascularized, and so presumably provides a reserve to meet any increase in myocardial oxygen demand after bypass, our findings suggest that the heart may be even more sensitive to changes in hemodynamics after bypass. Several previous studies support these findings. Mangano *et al.*³² have shown that the Frank-Starling mechanism is substantially limited after bypass, and that ventricular ejection progressively decreases with increasing preload. More recently, Mangano³³ has demonstrated that biventricular dysfunction occurs more frequently in the postbypass period and is more severe than in the prebypass period. Consistent with the presence of postbypass ventricular dysfunction is the prevalence of both ECG and echocardiographic ischemia during the immediate postbypass period.^{10,34} In

addition, postbypass RWMA appears to be predictive of adverse clinical outcome.¹⁰

Our finding that postbypass hemodynamic aberrations are frequently accompanied by RWMA has important clinical implications. Episodes of tachycardia and diastolic hypotension are more common in the postbypass period, and in combination may be particularly deleterious to the depressed ventricle and cause echocardiographic or ECG changes indicative of ischemia.^{10,34} In fact, we have found the incidence of myocardial ischemia as detected by ECG or TEE to be higher in the postbypass period. Clearly, a definitive clinical trial is necessary to determine whether better control of hemodynamics will lower the incidence of postbypass RWMA. Our findings do suggest that increasing coronary perfusion pressure and limiting tachycardia may be important in the immediate postbypass period when there are rapid fluctuations in supply and demand.

CLINICAL IMPLICATIONS

The relatively poor correlation of most RWMA with hemodynamic changes suggests that RWMA usually are not triggered by acute increases in myocardial oxygen demand. A more important etiology may be a primary decrease in myocardial oxygen supply. This hypothesis is supported by animal³⁵ and clinical studies³⁶ that demonstrate that ischemic regional ventricular dysfunction occurs frequently despite stable systemic hemodynamic parameters and normal left ventricular function. Multiple hypotheses have been proposed to account for these hemodynamically silent ischemic changes. First, Maseri³⁷ has suggested that coronary flow reserve may be both reduced and variable in patients with silent myocardial ischemia. Changes in coronary resistance at the site of a fixed stenosis may produce dramatic reductions in myocardial blood flow that result in ischemia when oxygen demand is low. Proof of the dynamic nature of coronary stenoses was provided by Brown *et al.*,³⁸ who demonstrated a 35% change in the luminal area of stenotic vessels during isometric exercise and nitroglycerin treatment, and even more dramatic changes in transstenotic coronary resistance. Coronary stenoses, therefore, likely behave in a dynamic fashion, rather than as a fixed flow limitation. Changes in stenosis size and vessel resistance therefore are not limited to patients with classic spasm, but also are typical of the majority of coronary stenoses.³⁹ Some investigators suggest that even without hemodynamic changes, localized spasm and thrombus formation superimposed on a significant coronary stenosis also may be an important cause of myocardial ischemia.^{12,40,41}

An additional explanation for the poor correlation between RWMA and hemodynamic changes is that mea-

surements of gross indices of myocardial oxygen supply and demand, such as HR and blood pressure, may be insensitive indicators of more subtle imbalances between supply and demand. This hypothesis is supported by studies in patients undergoing percutaneous transluminal coronary angioplasty.⁴² During balloon occlusion, peak negative and peak positive dP/dt occurred during the first few seconds, followed by abnormalities of systolic fractional shortening and increases in LV end-diastolic pressure, while HR and blood pressure were unchanged. Left ventricular pressure is therefore an earlier indicator of ischemic dysfunction than is HR or blood pressure measurement. A study by Smith *et al.*⁴³ suggests that increases in wall stress derived from TEE measurements are more frequently associated with RWMA than are hemodynamic changes. Patients undergoing carotid endarterectomy who received higher anesthetic concentrations supplemented with phenylephrine had higher wall stress and a three-fold greater incidence of RWMA and wall-thickening abnormalities than did those who received lower anesthetic concentrations to maintain similar SPBs and stump pressures. Therefore, reliance on hemodynamic monitoring alone in predicting myocardial ischemia is probably inadequate, especially in high-risk patients.

LIMITATIONS

1) Although the terms "TEE ischemia" and ECG ischemia" are used to indicate those changes suggestive of ischemia, without an absolute reference standard not all of these changes are necessarily indicative of ischemia. Among the nonischemic etiologies for RWMA are:

A) stunned or hibernating myocardium. Clinically, these are difficult to distinguish from ischemic myocardium.

B) areas of previous scarring unmasked by changes in afterload. Several observations make this latter etiology an unlikely explanation for the acute RWMA that we detected. First, most RWMA occurred in areas of myocardium with normal contraction (not previously scarred from myocardial infarction). Second, only marked changes in regional wall motion were considered "ischemic." A sudden increase in afterload is likely to cause changes in all segments rather than in just one. Third, although changes in loading conditions and contractility can influence regional left ventricular function,^{44,45} only 9% of all of our RWMA were preceded by a significant increase in PAD, and 14% by a significant increase in SPB, suggesting that global changes in loading conditions are unlikely causes for RWMA. However, since we have not directly measured regional changes in wall stress or contractility, we cannot rule out the contribution of these factors to the observed regional dysfunction.

C) tethering of nonischemic myocardium adjacent to ischemic or infarcted myocardium. Tethering accounts only for the overestimation of infarct size by echocardiography when compared to postmortem studies,⁴⁶ and would not create new RWMA in the absence of acute myocardial ischemia.

D) temperature heterogeneity after bypass. This can conceivably result in differences in regional contraction. However, although uneven cooling may occur after infusion of cardioplegia during bypass, rewarming is much more rapid and homogeneous and is an unlikely cause for regional dysfunction.

Validating RWMA or ST changes clinically is difficult, since they occur spontaneously and since there is no reference standard which allows continuous measurement. Indirect evidence suggests that the RWMA we observed were ischemic in origin. Our patients with persistent intraoperative RWMA had a significantly higher incidence of myocardial infarction than those without RWMA.^{10,11} More importantly, the locations of our intraoperative RWMA correlated with locations of postoperative myocardial infarction, indicating an ischemic etiology for these intraoperative TEE RWMA.¹⁰ Finally, we emphasize that the aim of our study was to relate hemodynamic changes to TEE RWMA and ECG ST changes, and not to ischemia *per se*.

2) Subtle hemodynamic changes may have occurred that are not reflected with our criteria of >20% alteration of control values. Stricter criteria to include any hemodynamic alterations >10% of control values may have demonstrated a stronger relationship with RWMA. However, choosing such criteria may not be clinically meaningful. Such narrow range control ($\pm 10\%$) is difficult, if not impossible, to achieve. Accurate measurement of myocardial oxygen demand and supply is difficult clinically. Of the three major determinants of myocardial oxygen demand, only HR can be measured directly. Direct measurement of contractility is impractical, and wall stress (volume \times chamber pressure \div wall thickness) can only be estimated with SPB measurement. Myocardial oxygen supply is determined by the coronary perfusion pressure and arterial oxygen content. Clinical measurement of coronary perfusion pressure is not practical. We chose DBP to estimate the driving pressure since the majority of blood flow to the left ventricle occurs during diastole.⁴⁷ We realize that HR, SBP, DBP, and PAD are only estimates of myocardial oxygen supply and demand, but they are the most useful clinical measurements available.

3) We used PAD as an estimate of LV filling pressure since pulmonary capillary wedge pressure could not be continuously measured and related to RWMA. Since PAD is greater than pulmonary capillary wedge pressure and since in the current study only 9% of RWMA were pre-

ceded by an increase in PAD, we can safely assume that similar results would hold for PCWP. The measurement of LV end-diastolic pressure would have been a more sensitive indicator of ischemia, since previous studies show that pulmonary capillary wedge pressure (and therefore pulmonary capillary wedge pressure) underestimates LV end-diastolic pressure when there is decreased ventricular compliance after acute myocardial infarction.²⁰ Although using LV end-diastolic pressure would have increased the correlation with ischemia, direct measurement of LV end-diastolic pressure is not practical.

4) Because of hemodilution, hemoglobin commonly decreases after bypass. We indirectly investigated whether a decrease in oxygen content secondary to hemodilution was related to an increase in RWMA during this period. No difference in postbypass hematocrits was detected between patients with and without postbypass TEE ischemic episodes. However, since we cannot continuously measure hemoglobin, we cannot rule out that TEE ischemic episodes may be precipitated by acute changes in hemoglobin that decrease myocardial oxygen supply.

5) Since we studied patients with documented coronary artery disease undergoing CABG surgery, the results of this study should be extrapolated with care to other patients and to those undergoing anesthesia for noncardiac surgery.

In summary, we found that most episodes of perioperative RWMA appear to be unrelated to gross hemodynamic changes. This finding suggests that a primary decrease in myocardial oxygen supply may be an important mechanism for most perioperative RWMA. In addition, neither pulmonary artery pressure measurements nor specialized indices (RPP and MAP/HR) appear to be useful in predicting onset of RWMA.

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