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Is the Pressure Rate Quotient a Predictor or Indicator of Myocardial Ischemia as Measured by ST-Segment Changes in Patients Undergoing Coronary Artery Bypass Surgery?

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Perioperative myocardial ischemia is associated with an increased risk of perioperative myocardial infarction (PMI). Several attempts have been made to define intraoperative hemodynamic predictors of myocardial ischemia. In a canine preparation with coronary stenosis, a pressure rate quotient (PRQ = mean arterial pressure/heart rate) less than one (PRQ < 1) indicated subendocardial myocardial ischemia. The authors tested this hypothesis in patients undergoing elective coronary artery bypass graft operation (CABG), using electrocardiogram (ECG) ST-segment changes (leads II/V_5) to diagnose myocardial ischemia. Sixty (n = 60) patients having CABG surgery were prospectively studied before initiation of cardiopulmonary bypass. Calibrated ECG leads II and V_5 (diagnostic mode) were monitored continuously and recorded with the use of a Hewlett-Packard computer ST-segment analyzer. In addition, arterial and pulmonary artery pressures were monitored. Ischemia was defined as *new*-onset ST deviation (≥1 mm from the baseline ECG). ECG and hemodynamic data were stored at 2-min intervals for subsequent computer analysis. Serial creatinine phosphokinase (CPK) × MB (%) determinations and 12-lead ECGs were collected for the initial 3 postoperative days. Of the 3,463 intervals (2 min) available for study, 3,322 (96%) were satisfactorily recorded for 60 patients. Ischemia occurred during 65 intervals in 9 patients (9 of 60), of which only 34% (22 of 65) were associated with a PRQ < 1 ($P < 0.01$). In contrast, there were 466 intervals during which PRQ was less than 1, but without ECG evidence of ischemia. Four (4 of 60) patients had PMIs, but in only 1 (1 of 4) was pre-CPB ischemia associated with a PRQ < 1. The authors conclude that PRQ < 1 is an insensitive indicator and predictor of myocardial ischemia in patients undergoing elective CABG. (Key words: Anesthesia: cardiac. Heart: coronary artery disease; ischemia, prediction of by pressure rate quotient; perioperative myocardial infarction; perioperative myocardial ischemia. Monitoring: electrocardiography; pressure rate quotient. Surgery: coronary artery bypass grafting.)

CARDIOVASCULAR DISEASE, with associated myocardial ischemia, infarction, and death, is a major health problem in the aging population. Of the five million patients with coronary artery disease (CAD), each year approximately 1.2 to 1.5 million will have myocardial infarctions, with the potential for 550,000 deaths.[1] Nevertheless, the incidence of perioperative myocardial ischemia has been difficult to assess. Several studies have reported the incidence to be as high as 74% in patients with known CAD undergoing major vascular surgery or coronary artery bypass graft (CABG) surgery.[2,3] The mortality after a perioperative myocardial infarction (PMI) is extremely high, and an association has been documented between perioperative myocardial ischemia and subsequent myocardial infarction.[4]

Given this high incidence of perioperative myocardial ischemia and the relationship to PMI, early indicators of myocardial ischemia might prompt institution of therapeutic measures to prevent the ischemia and potentially decrease the incidence of PMI. The electrocardiogram (ECG) is a commonly used monitor to detect myocardial ischemia in the operating room (OR). In a study in the ECG exercise laboratory, Blackburn and Katigbak reported that if a patient is simultaneously monitored with leads V_5 and II, approximately 96% of all ECG-detectable ischemic events can be diagnosed.[5] Recently, London *et al.* demonstrated intraoperatively that leads II, V_4, and V_5 are necessary to detect 96% of ischemic events.[6] However, because subtle ST-segment changes may go undiagnosed, computer-assisted ST-segment trend analysis of the intraoperative ECG has been advocated recently.[7] Several studies now have demonstrated the utility of ST-segment trend analysis for the early recognition of myocardial ischemia.[7,§] Controversy exists as to whether the ECG is an appropriate gold standard for measuring ischemia. Compared with other modalities such as transesophageal two-dimensional echocardiography (TEE), the ECG is a late indicator of ischemia.[8,9] However, TEE is expensive and requires extensive training. In addition, it is usually placed after laryngoscopy and intubation and is therefore not available during the critical periods during which a significant incidence of myocardial ischemia occurs.[4,10] Finally, Kaplan and Wells suggested that increased pulmonary capillary wedge pressure or development of prominent AC- or V-waves can indicate myocardial ischemia.[11] In subsequent studies, the pulmonary

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§ Kotter GS, Kotrly KJ, Kalbfleisch JH, Vucins EJ, Kampine JP: Myocardial ischemia during cardiovascular surgery as detected by an ST-segment trend monitoring system. Journal of Cardiothoracic Anesthesia 1:190–199, 1987.

capillary wedge pressure was an insensitive predictor of myocardial ischemia.[3,12] Thus, there is still a need for simple inexpensive methods to alert the anesthesiologist to the presence of myocardial ischemia.

Several hemodynamic correlates of myocardial ischemia have been evaluated. The product of the peak systolic blood pressure and heart rate—rate pressure product (RPP)—has been studied most extensively in the perioperative setting. However, it has been shown to be an unreliable predictor of myocardial ischemia during anesthesia.[13,14] Another index, the ratio of the systolic pressure–time index (SPTI) and the diastolic pressure–time index (DPTI), has also been shown to be ineffective as a predictor of ischemia for the anesthetized patient.[15]

Buffington reported that the pressure rate quotient (PRQ = mean arterial pressure [MAP]/heart rate [HR]) predicts ischemia in the nonfailing canine heart.[16] His experiments indicate that, if the PRQ decreases to less than one (PRQ < 1), there is relative hypoperfusion of the subendocardium and development of myocardial ischemia. Subsequently, Schwid and Buffington developed a computer model that supported the findings of the animal study.¶ As suggested by Merin, the PRQ theoretically is a better predictor of myocardial ischemia than the RPP, because it places greater emphasis on the role of HR in maintaining myocardial oxygen balance.** A study by Shiraki *et al.* concluded that PRQ < 1 was a useful indicator of myocardial ischemia in patients with CAD.†† However, their study had a small sample size (n = 13) and emphasized postbypass ischemia, a period notoriously difficult in which to detect ischemia.[17] Therefore, we prospectively studied the PRQ and its relationship to myocardial ischemia occurring before cardiopulmonary bypass (CPB) in patients undergoing an elective CABG operation.

Materials and Methods

This study was approved by the Human Investigation Committee. Sixty patients (34–88 yr), with multivessel CAD verified by cardiac catheterization, who were scheduled for elective coronary bypass surgery were admitted to this study. All patients received morphine sulfate 0.1 $mg \cdot kg^{-1}$ intramuscularly (im) and scopolamine 0.005 $mg \cdot kg^{-1}$ im 90 min before arrival in the OR, received their usual antianginal medications, and were transported to the OR while breathing oxygen delivered by nasal cannula at 3 l/min. Intraoperative monitoring included the following: electrocardiography (leads II and V_5 calibrated as 1 mV = 10 mm, diagnostic mode), pulse oximetry, end-tidal carbon dioxide concentrations, and arterial and pulmonary artery pressure catheters (inserted before anesthesia induction). In addition, all patients were monitored with the Hewlett-Packard computer processed ECG ST-segment analyzer (model HP 78534L), with a frequency response of 0.05–100 Hz, using leads II and V_5. This monitor measures the vertical difference between the isoelectric point (80 ms before the R-wave) and the ST-segment (120 ms after the R-wave). The settings for isoelectric and ST-segment points were adjusted for HR. The ST-segment deviations in leads II and V_5 are each updated and averaged over 15 s, and then displayed. Hard copy of the ECGs was obtained at specific times (during preinduction, induction/intubation, incision/sternotomy, and aortic cannulation) and whenever ST-segment changes (≥1 mm) appeared on the monitor. In addition, there was always one person continually viewing the monitor for ST-segment changes. On later review, the hard copies of ECGs were used to verify changes in the ST-segment deviation. The reviewers were not blinded to the clinical course. In all patients, general anesthesia was induced with sufentanil, 5–10 $\mu g \cdot kg^{-1}$ administered over a 10-min period during induction and endotracheal intubation. A sufentanil infusion (total, 15–20 $\mu g \cdot kg^{-1}$) was administered 60–90 min after induction of anesthesia. Pancuronium 0.1 $mg \cdot kg^{-1}$ was administered for paralysis. Based on clinical judgment, enflurane was administered for supplemental anesthesia. Patients were excluded from the study if they had abnormal myocardial repolarization. This includes any ST-T segment deviation for which a cause other than ischemia was documented (*e.g.*, digitalis effect, left ventricular hypertrophy, left bundle branch block).

ST-segment deviation, HR, and arterial, right atrial, and pulmonary artery pressures were recorded at 2-min intervals after placement of the monitors in the preinduction period (before induction of anesthesia) until initiation of CPB. Patients were considered to have new-onset myocardial ischemia if they had more than 1 min of ST-segment deviation that was ≥1 mm from their preoperative baseline ECG. Postoperatively, 12-lead ECGs were obtained daily for 3 days. Blood samples were obtained for measurement of creatinine phosphokinase (CPK) × MB% U/l fractions at the following times: immediately before CPB, on arrival in the intensive care unit, and every 8 h for 48 h. PMI was defined as a peak CPK × MB% greater than 80 U/l and ECG changes (new significant Q-waves and/or development of left bundle branch block).

The intraoperative period was composed of 2-min measurement-interval measurements. All data was stored

¶ Presented at the 1989 Annual Meeting of the Society of Cardiovascular Anesthesiologists, Seattle, Washington.

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on a Hewlett-Packard Vectra® computer on a Microsoft Excel® spread sheet. To clarify the definition of predictors and indicators of myocardial ischemia, the term predictor is used whenever the PRQ < 1 forecasts subsequent ischemia within 15 min. An indicator of myocardial ischemia identifies simultaneous occurrence of ischemia by ECG and PRQ < 1. The PRQ was compared with ST-segment depression ≥1 mm with the use of the Pearson chi-squared or Fischer's exact test ($P < 0.05$ significant).

Results

For the 60 patients (n = 60), 3,322 of the 3,463 intervals (2-min) available for study were satisfactorily recorded. Before CPB, 15% (9 of 60) of the patients had one or more ischemic (ECG) events. These 9 patients had a total of 65 ischemic intervals, of which only 34% (22 of 65) were associated with a PRQ < 1 (fig. 1). In addition, there were 466 nonischemic intervals (false-positives) with a PRQ < 1. Further, the PRQ was not only a poor indicator of myocardial ischemia, it had a very low predictive value. Comparison of the PRQ < 1 in ischemic patients (rather than by ischemic intervals) further suggests the PRQ is an insensitive indicator of myocardial ischemia (fig. 2).

Four patients (four of nine) arrived in the OR with new-onset myocardial ischemia as detected by ECG. In the remaining five patients (five of nine) in whom ischemia developed after arrival in the OR, only one of five (20%) had a PRQ < 1 in the 15 min preceding the onset of ECG-detected ischemia.

		ISCHEMIA (ECG)		
		Yes	No	Total
PRQ<1	Yes	22	466	488
	No	43	2791	2834
	Total	65	3257	3322

p<0.01
Sensitivity = 33.9%
Specificity = 85.7%
Positive Predictive Value = 4.5%
Negative Predictive Value = 98.5%

FIG. 1. Chi-squared analysis of perioperative intervals (2-min measurement) in which ischemia (ECG) occurred according to whether the PRQ was <1 or >1. Of the 65 ischemic intervals, only 22 (33.9%) had a corresponding PRQ <1. Also note that of the 3,257 intervals in which there was no ECG detected ischemia, there were 466 intervals in which the PRQ <1 was a false-positive predictor of ischemia. The positive predictive value is only 4.5%, which is too low for clinical application.

		ISCHEMIA (ECG)		
		Yes	No	Total
PRQ<1	Yes	6	30	36
	No	3	21	24
	Total	9	51	60

p=0.73
Sensitivity = 66.7%
Specificity = 41.2%
Positive Predictive Value = 16.7%
Negative Predictive Value = 87.5%

FIG. 2. Similar to figure 1, comparing ischemia detected by ECG *versus* PRQ <1 by *patient* rather than by 2-min measurement interval.

The distribution of the ischemic events for the nine ischemic patients relative to intraoperative periods was as follows: four of nine (44%) occurred during the preinduction period, five of nine (56%) during induction/intubation, one of nine (11%) during incision/sternotomy, and four of nine (44%) during aortic cannulation. The frequency distribution of ischemic intervals (n = 65) in the nine patients is shown in figure 3. The highest percentage of ischemic intervals is from four patients. The remaining five patients had fewer ischemic intervals.

As compared with the entire study population (n = 60), analysis of the patients with preoperative left ventricular ejection fraction (LVEF) greater than 55% (n = 22) reveals a subset of patients in whom PRQ < 1 better indicates ischemia ($P < 0.001$). In this subgroup (fig. 4) of the 13 ischemic intervals, 11 (85%) had a corresponding PRQ < 1. In the 996 intervals in which there was no

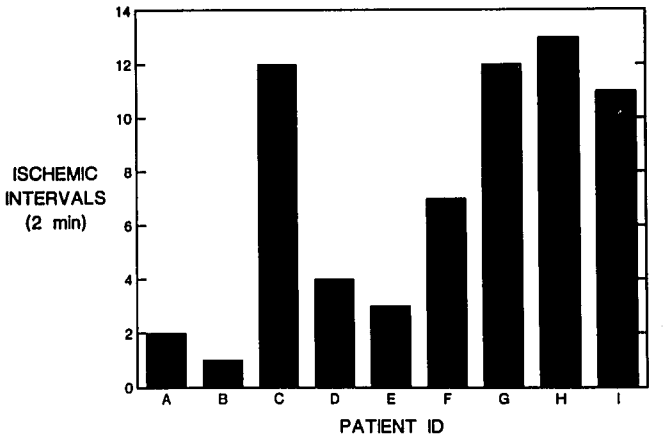

FIG. 3. Frequency distribution of the ischemic intervals in the 9 of 60 patients who had ischemia. Note that no patient dominated the ischemic measurements. ID = identification.

ISCHEMIA (ECG)			
	Yes	No	Total
PRQ<1 Yes	11	87	98
PRQ<1 No	2	909	911
Total	13	996	1009

p<0.01
Sensitivity = 84.6%
Specificity = 91.3%
Positive Predictive Value = 11.2%
Negative Predictive Value = 99.8%

FIG. 4. Analysis similar to figure 1 for the patients with LV ejection fractions greater than 55%. In this subgroup, the PRQ <1 is a more sensitive indicator of ischemia, 84.6% (11 of 13), and has better positive predictive value, 11.2% (11 of 98). However, positive predictive value is still very low.

ECG-detected ischemia, there were 87 intervals in which PRQ was less than 1 (false-positive). Patients with LVEFs > 55% (n = 22), as compared with the entire study population as a whole (n = 60), have higher sensitivity, 84.6% *versus* 33.9%; specificity, 91.3% *versus* 85.7%; and positive predictive values, 11.2% *versus* 4.5%, respectively. Although sensitivity and specificity for PRQ < 1 are improved in the subset with LVEFs > 55%, the positive predictive value is still too low (11.2%) for clinical application. Further, in comparison of mean pulmonary artery pressures (PAPm) >30 mmHg with those ≤30 mmHg,

ISCHEMIA (ECG)			
	Yes	No	Total
PRQ<0.75 Yes	3	40	43
PRQ<0.75 No	62	3217	3279
Total	65	3257	3322

p<0.01
Sensitivity = 4.6%
Specificity = 98.8%
Positive Predictive Value = 7.0%
Negative Predictive Value = 98.1%

FIG. 5. Chi-squared analysis of recorded intervals, *versus* PRQ <0.75. This analysis shows low sensitivity (4.6%) and positive predictive value 7.0%, but high specificity (98.8%) and negative predictive value (98.1%). PRQ <0.75 is not a better indicator of ischemia.

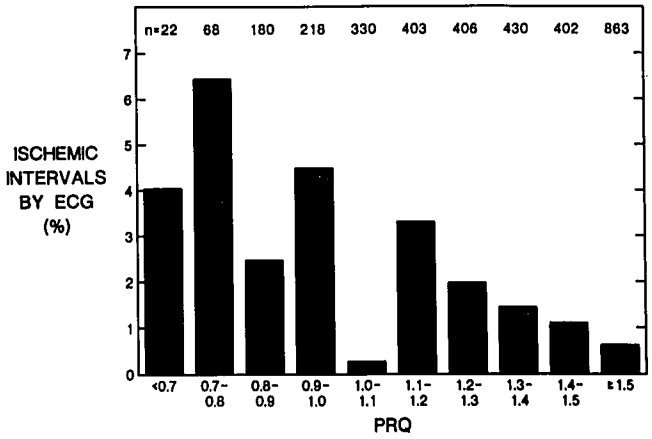

FIG. 6. The plot of various PRQs (<0.70 to ≥1.5) *versus* new onset ECG ischemia demonstrates that no level of PRQ is an adequate indicator of myocardial ischemia. N = the total number of 2-min recording intervals for each PRQ.

PRQ < 1 is neither statistically nor clinically a good indicator of ischemia ($P = 0.06$). Analysis of different PRQ values did not yield a PRQ that was a better indicator of ischemia. For example, a PRQ < 0.75 (fig. 5) had an extremely poor sensitivity of ischemia (4.6%; 3 of 65 intervals) and positive predictive value (7.0%), although it did have a high specificity (98.9%). Additional analysis of PRQ ratios (fig. 6) from PRQ < 0.7 to PRQ ≥ 1.50 do not show any specific value of PRQ as a better indicator of ischemia.

Postoperatively, 3 of 60 patients (5%) had PMI with both peak CPK × MB% >80 U/l and diagnostic ECG changes. This included 1 patient who had a CPK × MB product of 35 U/l and had new-onset left bundle branch block develop on postoperative ECGs. Myocardial infarction was diagnosed by the cardiologist. Of these 3 patients with PMI, only 1 had a PRQ < 1 at any time during the study period and only 2 had ECG-detected ischemia in the study period. There were no deaths.

Discussion

This study investigated the PRQ as an indicator and/or predictor of myocardial ischemia as compared with ischemia detected by computer-assisted ST-segment ECG trend analysis throughout the prebypass period in patients undergoing elective CABG surgery. We found that PRQ < 1 is a poor indicator or predictor of myocardial ischemia in patients with CAD undergoing elective CABG surgery. Only 34% of the ischemic intervals (ECG) occurred with PRQ < 1. Thus, a high percentage of all ischemic events were associated with PRQ > 1 (false-negatives) (fig. 1). The specificity of detecting ischemia by PRQ < 1 was 85.7% (2,279 of 3,257). Although these data are statistically significant ($P < 0.001$), the sensitivity and positive

predictive value demonstrate the PRQ to be less valuable clinically. This is further demonstrated in figure 6, in which there is a higher percentage of ischemic PRQs < 1 but there is a wide distribution of ischemic PRQs. In our data, PRQ < 1 indicates ischemia in only one third of the intervals associated with ischemia and predicts ischemia only 4.5% of the time. In contrast, PRQ < 1 is an excellent negative predictor of ischemia (99.9%). Thus, in our study, the PRQ is useful if there is no ischemia, but it is not a good clinical indicator if myocardial ischemia is present. The data in figure 2 demonstrate a similar pattern when the ischemia is related to the individual patient instead of 2-min measurement intervals. In addition, in review of the previous 15 min before an ECG ischemic event was detected, the PRQ < 1 ratio was not reliable as a predictor of ischemia.

The recent study by Shiraki *et al.*†† concluded that PRQ < 1 was an accurate indicator of myocardial ischemia and that this ischemia can be prevented by maintaining a PRQ < 1. The incidence of ischemia in their study is much higher than in ours: 46% (6 of 13 patients) *versus* 15% (9 of 60 patients), respectively. This increased incidence of myocardial ischemia may be a result of their inclusion of the post-CPB period—a time in which diagnosis of myocardial ischemia by ECG is notoriously difficult. As Leung *et al.* reported, the interpretation of ECG changes during this period is complicated by conduction, repolarization abnormalities, and ventricular pacing.[17]

A high percentage of cases of intraoperative ischemia are not associated with hemodynamic changes.[4,18,19] This was also observed in our study patients, because most of the ischemia events had very small or no increases in HR or MAP. Given this significant incidence of hemodynamically silent ischemia, it is understandable that reliable hemodynamic correlates of myocardial ischemia are difficult to derive.

The methods of this protocol have limitations. Our "gold standard" for the presence of myocardial ischemia is ST-segment deviation in leads II and/or V_5. Nonischemic ECG changes, such as left ventricular hypertrophy, digitalis effect, and electrolyte alterations (hypokalemia), can mimic ST-segment changes of ischemia. Thus, we excluded patients with abnormal myocardial repolarization that interfered with ST-segment analysis. Only new ST-segment depression ≥1 mm from the baseline ECG was considered to be diagnostic of myocardial ischemia. Serum potassium levels were frequently monitored, and any ST-segment deviation–related electrolyte changes were noted.

No monitor is both 100% sensitive and 100% specific for detection of myocardial ischemia.[3] The sensitivity and specificity of the ECG can be improved by use of a calibrated ECG in the diagnostic mode. As cited earlier, ischemic events may have been undetected because we monitored only leads II and V_5.[6] The addition of lead V_4 would potentially increase the sensitivity to ischemia from 80 to 96% in our study. This 16% increase would potentially yield only five more ischemic events but would not change the statistical significance of our findings.

Investigators have reported that TEE is superior to ECG for ischemic detection and suggest that TEE should be the "gold standard" for measuring myocardial ischemia.[20–25]‡‡ However, there are limitations of TEE for diagnosis of ischemia. The primary method used to detect ischemia with TEE is by the development of new regional wall motion abnormalities (RWMAs). As Ross reports, not all RWMAs represent ischemia.[26] Determinants of regional myocardial dysfunction depend on local conditions (*e.g.*, ischemia, scarring, systolic ventricular pressure, regional afterload, transmural "tethering," and interactions with adjacent regions). Further, the ischemic segment may be too small to be visualized by the plane of the ultrasonic beam.§§,¶¶ Finally, because the echoscope is usually inserted after induction and intubation, TEE may miss significant periods during which the risk for ischemia is great.[4,25] Studies using echocardiography as a gold standard have reported increases in ischemia detection between 20% and 300% as compared with those detected by the ECG.[17,19] Extrapolation of the data to our study would increase the positive predictive value of the PRQ < 1 from 9 to 67%, which is still inadequate for clinical use.

Buffington derived the PRQ in a canine preparation using systolic wall thickening as the standard against which the PRQ was compared.[16] The canine preparation in which extrinsic compression of tubing is used to decrease coronary blood flow may not be analogous to patients with CAD. In humans, these lesions are multiple and located throughout the coronary vasculature. Furthermore, in the Buffington study, the PRQ was predictive of ischemia in nonfailing canine hearts. Our patients had a wide range of left ventricular function (mean LVEF, 51%; range, 35–70%), without any evidence of overt congestive heart failure. In the subgroup of patients with LVEFs greater than 55%, the PRQ < 1 is a better indicator of ischemia. Even in this subset of patients, however, the PRQ < 1 is a poor positive predictor of ischemia (11%), with a value too low for any clinical application. However,

‡‡ Cahalan MK: Pro: Transesophageal echocardiography is the "gold standard" for detection of myocardial ischemia. Journal of Cardiothoracic Anesthesia 3:369–371, 1989.

§§ McCloskey G, Barash PG: Con: Transesophageal echocardiography is not the "gold standard" for detection of myocardial ischemia. Journal of Cardiothoracic Anesthesia 3:372–374, 1989.

¶¶ Thys D: The intraoperative assessment of regional myocardial performance: Is the cart before the horse? Journal of Cardiothoracic Anesthesia 1:273–275, 1987.

the LVEF is only a preoperative estimate of left ventricular function. In contrast, with the use of the PAPm in comparing the group with PAPm < 30 mmHg with the group with PAPm ≤ 30 mmHg, there are no clinical or statistical differences for the PRQ < 1 in this population subset. Therefore, our data suggest the PRQ < 1 is not a useful indicator of ECG-detected ischemia in the nonfailing heart. On a theoretic basis, PRQ < 0.75 (fig. 5), rather than PRQ < 1, should be a more robust indicator of myocardial ischemia. However, in our study this ratio was also a poor indicator of myocardial ischemia.

Considering the impact of CAD on our population, in terms of health care dollars and personal disability, there is need for a simple, inexpensive indicator or predictor of myocardial ischemia. Unfortunately, given the physiologic complexity of the determinants of myocardial oxygen supply and demand in a clinical setting and the high percentage of ischemic events that show little or no major hemodynamic changes, it is unlikely that a simple ischemia index, such as PRQ < 1, can aid in perioperative detection of myocardial ischemia in patients undergoing coronary bypass surgery.

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