

Hemodynamic Predictors of Myocardial Ischemia during Halothane Anesthesia for Coronary-Artery Revascularization

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The authors undertook a prospective study of 30 patients undergoing halothane anesthesia for coronary-artery revascularization to ascertain which clinically monitored hemodynamic variables—or combination of variables—associated with myocardial oxygen supply and demand best predict myocardial ischemia. Simultaneous recordings of electrocardiogram (lead II and V₅), systemic, central venous, pulmonary artery, and pulmonary artery occluded pressures were analyzed for correlation with ischemic episodes. Ischemia occurred with significant increases ($P < 0.0001$) in heart rate, central venous pressure, and pulmonary artery occlusion pressure and with significant decreases ($P < 0.0001$) in systolic and mean arterial blood pressure and in coronary perfusion pressure (mean arterial minus pulmonary artery occluded pressure). There was no correlation between ischemia and either hypertension (systolic blood pressures up to 200 mmHg) or the rate-pressure product.

Systemic systolic blood pressure, systemic mean arterial blood pressure, and coronary perfusion pressure as single determinants were the most useful to monitor in avoiding myocardial ischemia. A combination of systemic arterial blood pressure (systolic or mean) and filling pressure (central venous or pulmonary artery occluded) was generally as useful but not more so than the preceding single variables in avoiding ischemia. Rate-pressure product was not of value in this regard.

Patients were divided into three groups according to preoperative left ventricular (LV) function to determine whether pulmonary artery occluded pressure (PAOP) was more useful than central venous pressure (CVP) as either a predictor of ischemia or an index of cardiac filling: normal LV function (Group I), moderately abnormal LV function (Group II), and markedly abnormal LV function (Group III). PAOP offered no advantage over CVP for either purpose, except in some Group III patients. (Key words: Anesthetics, volatile; halothane. Blood pressure: hypertension; hypotension; measurement. Heart: compliance, ventricular; coronary occlusion, ischemia; myocardial function, anesthetics; oxygen consumption; pulse rate. Monitoring: blood pressure; central venous pressure; heart rate; pulmonary artery pressure. Surgery: cardiovascular, coronary artery bypass.)

A PRIMARY CONCERN in the intraoperative management of patients undergoing coronary-artery revascularization is the avoidance of ischemic injury to myocardium, because the benefits that derive from the surgical procedure may be offset by ischemic injury

sustained during the procedure. Surgeons employ hypothermia and pharmacologic cardioplegia in an attempt to preserve viable myocardium during cardiopulmonary bypass. Anesthesiologists attempt to avoid ischemia in the prebypass and postbypass periods by monitoring and manipulating certain hemodynamic variables associated with myocardial oxygen supply and demand. It has been stated that monitoring pulmonary artery pressure for the purpose of detecting ischemia is a major indication for the use of a balloon floatation catheter.¹ If such monitoring truly allows for either the prediction of, or the early detection of, myocardial ischemia, the anesthesiologist might be able to avoid ischemic injury supervenes. It would be helpful, therefore, to know which variables—or combination of variables—associated with oxygen supply and demand, when abnormal, best predict myocardial ischemia and would add more information to direct the choice of monitoring modalities. It also would be helpful to know at which point they become "abnormal."

Most investigations that have evaluated hemodynamic variables associated with myocardial oxygen supply and demand as predictors of myocardial ischemia have considered only coronary patients who are awake. Such studies do not consider that anesthesia and surgery may modify either the hemodynamic variables or their relationship with myocardial oxygen supply and demand. Relatively few investigations have attempted to evaluate such predictors of myocardial ischemia in anesthetized coronary patients.²⁻⁵ Moreover, none of the studies on anesthetized patients has quantitated predictive value⁶§ that quantitates the clinical applicability of a test. Therefore, using methods that do consider predictive values, we conducted a prospective investigation to ascertain which clinically accessible variables associated with myocardial oxygen supply and demand are most useful for predicting ischemia during coronary-artery revascularization.

Methods and Materials

We studied 30 patients undergoing coronary-artery revascularization. All 30 patients were taking propran-

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§ The predictive value of a test quantitates the likelihood that the test will predict accurately. It is a function of false-positivity, false-negativity, and the prevalence of the abnormal outcome (e.g., myocardial ischemia).

olol, in doses ranging from 40–320 mg/day (mean dose, 136 mg/day). Only three patients were taking digitalis, 0.25 mg/day. All patients had exhibited ischemic ST-segment changes before the day of operation, during either stress testing or spontaneous angina, and all patients (even those taking digitalis) had isoelectric ST-segments before anesthetic induction.

We established monitoring before anesthetic induction with an ECG lead (II or V₅),^{8–10} which had revealed ischemic ST-segment changes previously during stress testing or spontaneous angina, a radial arterial cannula, and a triple lumen pulmonary artery (PA) catheter. The arterial blood pressure (BP), central venous pressure (CVP), and pulmonary artery occluded pressure (PAOP) were measured by Gould[†] Statham P23 1d transducers, and recorded every 60 s for three consecutive respiratory cycles on a Gould 260 Brush Recorder. The ECG (1 mV = 10 mm) was recorded in the same manner.

We defined ischemia as ST-segment depression of at least 1 mm, measuring the ST-segment 80 ms after the J-point. Using 2-mm ST-segment criteria may increase the incidence of false-negative interpretations more than it would decrease the incidence of false-positive interpretations.^{11**} We evaluated seven variables associated with myocardial oxygen supply and demand as predictors of ischemia. Oxygen supply variables included mean arterial blood pressure (MAP) and coronary perfusion pressure (CPP). Oxygen demand variables included heart rate (HR), systolic arterial blood pressure (BPs), rate–pressure product (RPP), CVP, and PAOP. We defined RPP as “BPs × HR,” and CPP as “MAP – PAOP” or “MAP – CVP.”

Each value for HR and BPs was tabulated as the average of five consecutive values as read from the strip recording. CVP and PAOP were tabulated as the average of three consecutive end-expiratory values, also as read from the analog strip recording.¹² Baseline BPs, MAP, HR, and RPP were taken as the average of at least six measurements recorded before induction of anesthesia.

The study periods were from anesthetic induction until 5 min after sternotomy and for the first 10 min following discontinuation of cardiopulmonary bypass. We thus included the critical periods of anesthesia and surgery during which ischemia is most likely to occur. In this manner, we collected approximately 40 sets of measurements per patient (1,216 total measurements).

Approximately 90 min after premedication with intramuscular morphine sulfate, 0.1 mg/kg, and scopolamine, 0.07 mg/kg, anesthesia was induced by mask with halothane in a mixture of 50% oxygen and nitrous

TABLE 1. Mean Baseline Values and Percentage Changes During Ischemia and Nonischemia

Variable	Mean Baseline Value (95% Limits)	Percentage Mean Change from Baseline	
		Nonischemia (95% Limits)	Ischemia (95% Limits)
CPP (MAP–PAOP) (mmHg)	79 (77–82)	–5* (–6––3)	–18* (–22––14)
BP (mmHg)	121 (117–126)	13* (11–14)	0* (–4–+3)
MAP (mmHg)	89 (86–92)	3* (2–4)	–6* (–10––3)
HR (beats · min ^{–1})	68 (66–70)	0* (–1)	13* (10–17)
RPP (beats · min ^{–1} · mmHg)	8,313 (7,939–8,687)	14† (8–21)	10† (4–15)
PAOP (mmHg)	9.5 (8.6–10.5)	73* (69–78)	84* (76–91)
CVP (mmHg)	5.1 (4.5–5.7)	118* (112–124)	158* (144–173)

* Statistically significant, $P < 0.001$ by analysis of variance.

† Not significant.

oxide. Laryngoscopy was facilitated by a 0.2% succinylcholine infusion, and the trachea was sprayed with 4 ml of 4% lidocaine solution. The patient was ventilated further by mask until hemodynamic conditions were judged to be favorable for endotracheal intubation. Following intubation, anesthesia was maintained with halothane and nitrous oxide in at least 50% oxygen. Pancuronium was used for muscle relaxation, and ventilation was controlled mechanically. Arterial oxygen tension was maintained above 100 mmHg, and arterial carbon dioxide tension between 33 and 42 mmHg. The concentration of halothane and the choice, dose, and timing of administration of inotropes and vasodilators were at the discretion of the anesthesiologist, who was not a member of the study team.

Absolute values and percentage change for each variable during ischemia were compared to those during nonischemia using a regression approach to analysis of variance in which the individual patient and given minute of observation were examined as co-variants simultaneously; $P < 0.05$ was considered statistically significant. We then used chi-square analysis to select a single point and percentage change for each variable such that values on one side of that point had the highest association with ischemia and values on the other side of that point had the highest association with nonischemia.¹³ For example, we considered BPs ≤ 90 mmHg or $> 30\%$ below baseline to constitute a *positive test*, which predicted the abnormal outcome, ischemia. Values at or greater than these test values constituted a *negative test*, which predicted the normal outcome, nonischemia. Using discriminant analysis, we then evaluated the ability of these test values singly and in combination, to predict the presence or absence of ischemia.¹⁴

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** Use of 2-mm criteria revealed only two episodes of ischemia in 1,216 observations in 30 patients.

TABLE 2. Predictability and Efficiency of Test Values and Percentage Change from Baseline

Variable	Test Value	Percentage Change from Baseline	Predictive Value of Positive Test (%)	Predictive Value of Negative Test (%)	Efficiency (%)
CPP (MAP-PAOP)	≤50 mmHg*	-40†	73	85	84
BPs	≤90 mmHg*	-30†	79	84	84
MAP	≤65 mmHg*	-30†	62	84	83
HR	≥80 beats · min ⁻¹	+20†	35	87	73
PAOP	≥15 mmHg*	+76‡	24	85	55
CVP	≥10 mmHg*	+138§	24	87	53

* $P < 0.00001$.† $P < 0.0001$.‡ $P < 0.0037$.§ $P < 0.0005$.

For the purpose of comparing the usefulness of CVP and PAOP relative to the extent of left ventricular (LV) dysfunction, we divided the patients into three groups of 10: Group 1 patients had normal LV function, defined as an LV end-diastolic pressure (LVEDP) not greater than 12 mmHg either before or after coronary angiography, an ejection fraction (EF) above 0.50, and normal LV segmental wall motion. Group 2 patients had moderately abnormal LV function defined as a preangiographic or postangiographic LVEDP greater than 12 mmHg but a normal EF and normal segmental wall motion. Group 3 patients had markedly impaired LV function, defined as a preangiographic LVEDP greater than 12 mmHg, an EF below 0.50, and dyssynchronous wall motion. No patient had a preoperative CVP above 7 mmHg.

Results

Ischemia was present intermittently in 20 of the 30 patients during 230 (18.9%) of the 1,216 measurement periods. There were 35 ischemic episodes in Group 1 patients, 71 episodes in Group 2 patients, and 124 episodes in Group 3 patients. The likelihood of intraoperative ischemia is related to the extent of preoperative LV dysfunction ($P < 0.0001$ by chi-square analysis).

The transition from nonischemia to ischemia was associated with a highly significant change in the mean values of all variables except RPP (table 1). Ischemia was associated with significant *increases* in HR, PAOP, and CVP, and with significant *decreases* in BPs, MAP, and CPP. Nearly identical results were obtained for CPP when derived from PAOP and CVP. The 5 mmHg difference in baseline values reflects the difference between baseline CVP and PAOP. Chi-square analysis failed to reveal an association between ischemia and systemic hypertension, even with BPs as high as 200 mmHg. Table 1 also compares mean baseline values of each determinant with the mean values observed during ischemia and suggests that while relatively large percentage increases from baseline PAOP and CVP were well tolerated, relatively small percentage decreases from base-

line BPs and MAP—indices of oxygen supply—were tolerated poorly. That is, although ischemia tended to not occur until PAOP and CVP increased 84% and 158%, respectively, it tended to occur with only a 6% decrease in MAP. Ischemia was associated with decreases (18%) in CPP, another index of oxygen supply.

Table 2 displays the test values for each variable, above which (a positive test for HR, PAOP, CVP) or below which (a positive test for BPs, CPP, MAP) ischemia is more likely to, but will not necessarily, occur. Similarly, ischemia is less likely to but still may occur with a negative test, *i.e.*, below the appropriate test values for HR, PAOP, and CVP, or above the test values for BPs, CPP, and MAP. Table 2 also displays the predictive values of positive and negative tests, as well as the predictive *efficiency* of each variable (true positives + true negatives ÷ total responses).⁶ The latter is the best overall index of a variable's ability to predict accurately. For example, comparing the actual outcome of ischemia or nonischemia with the outcome predicted by a BPs above or below 90 mmHg, our model was correct 84% of the time. Negative tests had uniformly high predictive values, being true-negative 84–87% of the time. Positive tests, on the other hand, exhibited much lower predictive values. For example, the most accurate positive test, BPs < 90 mmHg, was a "false alarm" 21% of the time while MAP ≤ 65 mmHg was a false alarm 38% of the time, and both CVP ≥ 10 mmHg and PAOP ≥ 15 mmHg 76% of the time.

A more logical way to evaluate a variable's "true" predictive efficiency is to compare its efficiency with that of a prediction made purely by chance. With this in mind, we calculated a 69% probability of making an accurate prediction of ischemia or nonischemia by chance.^{††} It is apparent that only BPs, CPP, and MAP offer significant improvement over a purely chance prediction.

†† The likelihood that a chance prediction will be accurate is 50% only if the prevalence of the predicted event is 50% (as in the chance that a coin-flip with turn up "heads"). Therefore, we calculated the likelihood of making an accurate, chance prediction relative to the 18.9% prevalence of ischemia.⁷

RPP is not included in table 2 because we were unable to select a clinically relevant test value point by chi-square analysis. RPPs of 12,000 and 17,000, the former value often cited as a clinically important predictor of intraoperative ischemia,⁵ had fairly high chi-square values, but their negative tests were falsely-negative 52–58% of the time.

Table 3 displays predictive values of positive and negative tests, as well as overall efficiency, for combinations of variables. The BPs–CVP pair was just as efficient as the BPs–PAOP pair, and neither pair improved the overall predictive efficiency of BPs alone. Importantly, however, the negative tests of both pairs had higher predictive values than the negative test of BPs alone; specifically, the likelihood of a false-negative result decreased from 16% to 9%. No combination of variables improved, and some combinations actually decreased, the predictive values and efficiency of the “best” variables in the group.

Since CVP and PAOP had similar predictive values and efficiencies, we performed two additional tests to ascertain whether the relative usefulness of CVP and PAOP as predictors of ischemia is modified by the extent of preoperative LV dysfunction: 1) We counted the number of times in Groups 1, 2, and 3 that elevations of CVP or PAOP were the *only* predictors of ischemia (*i.e.*, when all other variables yielded false-negative tests) and, 2) We subjected the CVP–PAOP relationship to linear regression analysis in each group in order to determine how accurately CVP predicts PAOP. An isolated elevation of PAOP was never the only predictor of ischemia for Group 1 or Group 2 patients (table 4); in fact, an isolated CVP elevation appeared to be a better predictor for Group 1 patients, constituting the only warning in 40 per cent of ischemia episodes. An isolated elevation of CVP may also be a better predictor of ischemia in Group 3 as a whole, predicting a total of six ischemic episodes in two patients, as opposed to two episodes in a single patient predicted by PAOP. That the PAOP did occasionally provide the only warning of ischemia may be clinically important for preventing ischemic injury in some patients with markedly impaired LV function. Table 4 also reveals a moderately significant correlation between CVP and PAOP in Group 1; there were poorer correlations between the two variables in Groups 2 and 3.

Discussion

The definition of ischemia based on electrocardiographic changes has been shown to correlate with other indices of ischemia.^{15,16} These include angina, abnormal myocardial lactate metabolism, and abnormal LVEDP.^{17,18} We evaluated each variable as a useful monitor for avoiding ischemia, not merely as an efficient

TABLE 3. Predictive Values and Overall Predictive Efficiencies of Combinations of Hemodynamic Variables

Determinant	Predictive Value of Positive Test (%)	Predictive Value of Negative Test (%)	Efficiency (%)
BPs, CVP	76	91	83
BPs, PAOP	76	91	83
MAP, CVP	56	84	82
MAP, PAOP	56	84	82
HR, BPs	36	88	72
HR, CVP	33	84	72
HR, PAOP	33	84	72
HR, CVP, BPs	38	88	75
HR, CVP, BPs, CPP	37	88	74
HR, CVP, BPs, PAOP, MAP	36	80	73

predictor of ischemia. Our data led us to conclude that during halothane anesthesia for coronary-artery revascularization, BP, MAP, and CPP were the most useful variables to monitor in order to avoid myocardial ischemia.

Ischemia associated with impaired myocardial oxygen supply seems to be more prevalent during halothane anesthesia than during morphine anesthesia where ischemia is related more often to increased oxygen demand.¹⁹ BPs \leq 90 mmHg or greater than 30% below baseline offered the advantage of being the most reliable positive tests; all three oxygen supply variables had virtually identical efficiencies and predictive values of negative tests. Whereas efficiency is the best statistical index of a variable's ability to predict ischemia, the most desirable clinical attribute is a high predictive value of a negative test. This is because the higher the predictive value of a negative test, the lower the likelihood that a false-negative result will mislead the clinician into allowing ischemia to persist untreated.‡‡

Low values of BPs, MAP, and CPP suggest impaired myocardial oxygen supply. The best way to avoid ischemia during halothane anesthesia, therefore, may be to maintain myocardial oxygen supply via adequate systemic and coronary perfusion pressures. Our data suggest that we should not allow BPs to drop below 90 mmHg or 30% below baseline or MAP to drop below 65 mmHg or 30% below baseline. The absolute value is usually the more conservative guideline with percentage change perhaps more appropriate for hypertensive patients.

The most useful pairs of variables to monitor in order to avoid myocardial ischemia were BPs–CVP, BPs–

‡‡ For example, a variable with a high overall efficiency of 85% but only a 60% predictive value of its negative test would be an unacceptable clinical tool, owing to the 40% chance that it could fail to alert the clinician to the presence of ischemia. On the other hand, although CVP has a low overall efficiency of 60%, its usefulness as a clinical tool is enhanced by the high (84%) predictive value of its negative test.

TABLE 4. Comparison of CVP and PAOP as Predictor of Ischemia and of Each Other in Each LV Function Group

	Group 1	Group 2	Group 3
Ischemic minutes (n)	35*	71*	124*
PAOP <i>only</i> predictor	0	0	2 episodes (1 patient)
CVP <i>only</i> predictor	14 episodes (4 patients)	0	6 episodes (2 patients)
CVP-PAOP regression	n = 411 r = 0.666 y = 0.639 × +7.82 P < 0.001	n = 413 r = 0.549 y = 0.683 × +8.39 P < 0.001	n = 392 r = 0.539 y = 0.928 × +6.82 P < 0.001

* P < 0.0001 by chi-square analysis comparing presence of ischemia and group.

PAOP, MAP-CVP, and MAP-PAOP. Pairing either CVP or PAOP with BPs did not enhance the efficiency (83 vs. 84%) of BPs alone, but the predictive value of the pairs' negative tests increased from 84 to 91%, thereby halving the likelihood of false-negative results. No other pairs or combinations of multiple variables equaled the usefulness of the BPs-CVP and BPs-PAOP pairs.

RPP was of no value in predicting myocardial ischemia in our patients. The inability of RPP to predict ischemia parallels the same inability of BPs as high as 200 mmHg. Whereas an "abnormal" (elevated) RPP has usually been considered to be the product of *hypertension* and tachycardia, we found ischemia much more likely to develop with *hypotension* and tachycardia. Accordingly, we frequently found ischemia occurring with a traditionally "normal" RPP (<12,000) and nonischemia occurring with a traditionally "abnormal" RPP (>12,000).

Introduced in 1957 as an index of myocardial oxygen consumption ($\dot{M}\dot{V}O_2$) in dogs, RPP somehow became accepted as a predictor of ischemia in man.²⁰ On the basis of a small study showing the development of ischemia in anesthetized (morphine-diazepam-N₂O) coronary patients whose RPP exceeded 12,000, this value became accepted as the critical level for the development of ischemia in all anesthetized coronary patients.²¹ The authors emphasized, however, that ischemic patients had significantly higher HRs than did patients who were not ischemic. Unfortunately, they did not resolve the question of whether ischemia developed secondary to the high RPP or to the tachycardia *per se*. In 1978, Loeb *et al.* showed that at similar high levels of $\dot{M}\dot{V}O_2$, tachycardia is more likely than hypertension to produce myocardial ischemia in coronary patients who are awake.²² They suggested further that "hypertension *per se* may play a relatively minor role in precipitating myocardial ischemia in patients with fixed coronary artery obstruction." In 1979, Sonntag *et al.* found poor correlation between RPP and $\dot{M}\dot{V}O_2$ in healthy humans anesthetized with halothane.²³ RPP does not include an index of myocardial contractility, and anesthetic-in-

duced changes in contractility can greatly alter $\dot{M}\dot{V}O_2$ without producing changes in HR or BP.²⁴ Moreover, an increase in ventricular volume will increase $\dot{M}\dot{V}O_2$ without altering RPP. In a more recent publication, Kissen *et al.* showed that RPP did not correlate with ischemia in anesthetized dogs with acute localized coronary artery obstruction.²⁵ He also voiced concern that ischemia may co-exist with a "normal" RPP (<12,000) associated with low BP and high HR and suggested that treating such ischemia by raising the BP and, in turn, the RPP, can be expected to correct the ischemia.

PAOP offered no advantage over CVP, either as a predictor of ischemia or as an index of cardiac filling, except in certain patients with markedly impaired LV function. CVP and PAOP were virtually interchangeable predictors of ischemia for patients in Groups 1 and 2. This was true when the two variables were considered alone, in combination, or as derivatives (*e.g.*, CPP). The correlation between CVP and PAOP was significant (P < 0.001) in all three groups. These findings suggest that clinically important "disparity of ventricular function"²⁶ is not universal among anesthetized patients with coronary-artery disease anesthetized with halothane and are consistent with previous observations in anesthetized humans that changes in PAOP—at both normal and abnormal levels—may be accompanied by proportional changes in CVP.^{27,28}

This conclusion has important implications for the clinician who daily must re-evaluate the controversy surrounding routine PA catheterization of patients undergoing coronary-artery revascularization. There are no universally accepted criteria for PA catheter use in such patients. Some clinicians catheterize only selected patients, while others accept Swan's policy that if a CVP catheter is considered, a PA catheter should be used.²⁹

There are important questions as to the balance of benefit and risk in applying PAOP monitoring.^{2,28-33} The present study suggests more specific applicability when taken from the point of view of predictability of ischemia. These results support Mangano's findings that PAOP measurements are of greatest significance in the subgroup of patients who have markedly impaired LV

