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Indices of Myocardial Oxygenation during Coronary-artery Revascularization in Man with Morphine Versus Halothane Anesthesia

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A prospective study in 12 adult male patients undergoing coronary-artery revascularization was conducted to compare the effects of a morphine versus a halothane anesthetic technique on several indices of myocardial oxygen supply and demand. Indices reflecting myocardial contractility, preload, afterload, and heart rate were measured. Undesirable increases in systemic and pulmonary capillary wedge pressure were minimized using sodium nitroprusside as needed. In the period after sternotomy but before revascularization, patients anesthetized with morphine (mean 2.1 mg/kg) had significant ($P < .05$) increases in rate–pressure product, tension–time index, blood pressure, and heart rate, as well as relative myocardial ischemia, evidenced by significant ST-segment depression in the V_5 lead of the EKG and a decreased diastolic pressure–time index/tension–time index compared with patients anesthetized with halothane (mean .75 per cent inspired). Few difficulties associated with myocardial depression were seen in patients anesthetized with halothane. Halothane, at least in a well-monitored environment, is safe for use in patients without severe ventricular dysfunction undergoing coronary-artery revascularization. (Key words: Anesthesia: cardiovascular. Anesthetics, intravenous: morphine. Anesthetics, volatile: halothane. Heart: oxygen consumption; myocardial function; contractility; vascular pressures. Surgery: cardiac.)

THE USE of an anesthetic agent that depresses myocardial contractility in patients who have coronary-artery disease is a current subject of controversy.[1–6] The clinical impression and objective evidence[7] that morphine anesthesia maintains stable cardiovascular signs served to popularize the use of a morphine technique for all types of open-heart procedures.[8] In light of new information concerning the determinants of myocardial oxygen consumption and supply, the wisdom of using morphine, with its propensity for causing hypertension,[9] for coronary-artery surgery has been questioned,[1,2] and the use of halothane has gained in popularity.[4]

Although both morphine- and halothane-based anesthetic techniques continue to be widely used for coronary-artery revascularization, there has been no prospective clinical study comparing their effects on myocardial oxygenation. Such a comparison could be important to the large number of patients with coronary-artery disease who receive anesthesia both for coronary-artery revascularization and for other procedures. We, therefore, studied two groups of patients scheduled for coronary-artery bypass grafting, one anesthetized with a halothane–nitrous oxide–oxygen technique and the other with a morphine–nitrous oxide–oxygen technique, in order to compare several indices of myocardial oxygenation.

Materials and Methods

After informed consent had been obtained, 12 adult male patients who had ischemic heart disease necessitating coronary-artery revascularization were alternately placed into two groups. Only patients without severe ventricular dysfunction (no history of congestive heart failure, pre-angiogram pulmonary capillary wedge pressure <14 torr during catheterization, and ejection fraction >50 per cent) were considered for the study. Patients were premedicated with morphine, 0.1 mg/kg, and scopolamine, 0.4 mg, and brought to the operating room, where two large peripheral venous cannulas were inserted, a radial artery was percutaneously cannulated, and a #7 thermodilution Swan-Ganz catheter was placed by a modified Seldinger technique via a right internal jugular approach. Electrocardiogram (including lead V_5), radial and pulmonary arterial pressures, pulmonary capillary wedge pressure (PCW), esophageal temperature, and the second heart sound (obtained by phonocardiogram) were recorded on an eight-channel Hewlett-Packard recorder. Biotronix LVDT transducers were used. Only tracings judged technically adequate were included in the data. The protocol had been approved by the Human Studies Committee.

Baseline values were obtained and anesthesia induced. In one group of patients, morphine, 5–10 mg/min, was given intravenously to a mean total dose of 1.2 mg/kg while the patient breathed nitrous oxide–oxygen, 50 per cent each. Diazepam, 5 mg, iv, was given to minimize excitement. When the lid reflex was lost, pancuronium, 0.08 mg/kg, was given to facili-

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tate control of ventilation and endotracheal intubation. Five minutes later, lidocaine, 140 mg, was administered topically to the trachea. After another 3-min interval, the trachea was intubated. Additional 10-mg increments of morphine were given as necessary to an average total dose of 2.1 mg/kg. Nitrous oxide was discontinued about 3 min before cardiopulmonary bypass and not resumed until hemodynamic stability was achieved after weaning from cardiopulmonary bypass. Diazepam, 10 mg, was given at the onset of bypass.

In the other group of patients, anesthesia was induced by mask with nitrous oxide–oxygen, 50 per cent each, to which halothane (1.5 per cent maximum inspired concentration) was added. Diazepam, pancuronium, and lidocaine were given as described above. The inspired concentration of halothane was adjusted according to arterial pressure, PCW, and level of surgical stimulation, and was decreased or discontinued during atrial and aortic cannulation. Halothane, 0.5 per cent, was given via the oxygenator during cardiopulmonary bypass so long as the mean blood pressure was greater than 50 torr, but was discontinued approximately 10 min before termination of bypass. When circulatory stability after weaning from bypass had been achieved (approximately 5–10 min), nitrous oxide, 50 per cent, and halothane were reinstituted.

Patients manifesting systolic hypertension more than 20 per cent above normal preoperative levels, a rate–pressure product exceeding a preoperative anginal threshold documented by graded exercise testing, or any hypertension associated with an increased PCW or ST-T-wave changes were treated to bring systolic blood pressures to within 10 per cent of preoperative levels. Patients receiving halothane were treated with increased concentrations of halothane to a maximum of 1.5 per cent inspired whenever PCW was less than 15 torr. When blood pressure could not be decreased without increasing the PCW to more than 15 torr, sodium nitroprusside was added. Hypertension in patients anesthetized with morphine was treated with additional increments of morphine to a maximum dose of 2.5 mg/kg. Sodium nitroprusside was added whenever hypertension persisted.

Measurements were made with the patient awake, 10 min after intubation, 5 min after sternotomy, and 30 and 60 min after the end of cardiopulmonary bypass. Direct measurements taken at end-expiration included mean blood pressure, heart rate, PCW, central venous pressure, and cardiac output. Indices derived from standard equations[10] included cardiac index, systemic vascular resistance, stroke volume index, and left ventricular stroke work index. The remaining measurements were calculated at a later time from the recordings. Tension–time index and diastolic perfusion time index/tension–time index ratio (DPTI/TTI) were calculated by planimetry from the area under three consecutive beats on the radial arterial tracing recorded at 100 mm/sec. Systolic time intervals including total electromechanical systole (QS_2), left ventricular ejection time (LVET), pre-ejection period (PEP), $1/PEP^2$, and PEP/LVET were derived by previously described methods[11] using the arterial tracing, electrocardiogram, and the second heart sound, recorded initially by phonocardiogram from the precordium and subsequently from an esophageal stethoscope. Although a time lag between recording sites has been reported,[12] the two positions for recording gave identical values with our system. ST-segment depression was measured in the V_5 lead of a calibrated EKG tracing .08 sec after the J point.[13] ST-segment deviation for five consecutive beats was recorded to encompass one respiratory cycle. Cardiac output was measured at least in duplicate by thermodilution, using an Edwards computer. Thermal tracings were recorded to observe for artifacts. Reproducibility was within ±5 per cent. Arterial blood gas values were measured frequently and ventilation adjusted to maintain arterial blood P_{O_2} greater than 90 torr, P_{CO_2} 35–40 torr, and pH 7.38–7.45.

Statistical analysis was performed using the Student t test. Differences were considered significant when $P < .05$. Values are presented as means ± SEM.

Results

The two groups of patients were similar with respect to age, history, ventricular function, and number of vein grafts. No patient had any memory of events during anesthesia. All patients had uncomplicated postoperative courses except one patient anesthetized with morphine, who experienced failure of several organ systems. Five of six patients anesthetized with morphine received nitroprusside (15–100 μg/min) to decrease afterload and preload, while two of six patients receiving halothane received nitroprusside (10–60 μg/min).

There was a tendency for PCW to increase with induction of anesthesia (table 1). Only in patients receiving halothane was the change statistically significant. After sternotomy, several patients anesthetized with morphine had marked increases in PCW, but because of large individual variations the change was not statistically significant. Wedge pressure after bypass was not altered significantly by either anesthetic agent.

Patients receiving halothane showed decreased contractility with induction of anesthesia, as evidenced

TABLE 1. Changes in Preload

	Pulmonary Capillary Wedge Pressure (torr)				
	Awake	10 Minutes after Intubation	5 Minutes after Sternotomy	30 Minutes after Bypass	60 Minutes after Bypass
Morphine	11 ± 7	12.3 ± .6	15.5 ± 3.2	14.3 ± 1.9	13.3 ± 1.0
Halothane	11 ± 1	15.2 ± 2.8*	12.0 ± .7	12.0 ± 1.4	11.2 ± 1.2

* Significant difference from control, $P < .05$.

TABLE 2. Changes in Indices Reflecting Myocardial Contractility

	Control	10 Minutes after Intubation	5 Minutes after Sternotomy	30 Minutes after Bypass	60 Minutes after Bypass
Cardiac index (l/min/m²)					
Morphine	2.8 ± .1	2.7 ± .1	2.4 ± .3*	3.0 ± .3	2.8 ± .2
Halothane	2.9 ± .2	2.6 ± .3	2.4 ± .3*	3.5 ± .4*	2.6 ± .2
Stroke volume index (ml/min/m²)					
Morphine	47 ± 5	44 ± 4*	33 ± 6*	31 ± 4*	31 ± 3*
Halothane	48 ± 3	34 ± 4†*	31 ± 4*	37 ± 4*	27 ± 2*
Left ventricular stroke work index (ml/min/m²)					
Morphine	52 ± 4	49 ± 5	40 ± 7*	30 ± 5*	34 ± 4*
Halothane	59 ± 4	37 ± 4†*	35 ± 3*	43 ± 4†*	31 ± 2*
PEP/LVET					
Morphine	.33 ± .03	.33 ± .04	.33 ± .05	.38 ± .05	.33 ± .03
Halothane	.32 ± .02	.43 ± .06†*	.42 ± .06†*	.26 ± .01†*	.38 ± .05
1/PEP²					
Morphine	110 ± 31	122 ± 31	115 ± 31	83 ± 13	102 ± 30
Halothane	113 ± 15	64 ± 12†*	67 ± 11*	130 ± 13†*	90 ± 20
QS_2 index (msec)					
Morphine	565 ± 7	578 ± 10*	587 ± 8	558 ± 12	558 ± 7
Halothane	543 ± 15	597 ± 13†*	581 ± 10*	565 ± 14*	548 ± 3

* Significant difference from control, $P < .05$.
† Significant difference between anesthetic agents, $P < .05$.

by decreases in stroke volume, left ventricular stroke work, and 1/PEP², and an increased PEP/LVET (table 2). Incision and sternotomy resulted in little further change. Thirty minutes after bypass, increases in 1/PEP² and cardiac index occurred with a decrease in PEP/LVET ratio, indicating increased myocardial contractility. By 60 min after bypass, with deeper levels of anesthesia, significant myocardial depression was again evident.

Patients anesthetized with morphine showed a different pattern (table 2). No change occurred with induction of anesthesia, but following sternotomy, there were decreases in contractility, as evidenced by decreases in cardiac index, stroke volume index, and left ventricular stroke work index, but without change in the systolic time intervals. Unlike patients anesthetized with halothane, patients receiving morphine showed decreased contractility 30 min after bypass. At 60 min contractility had improved toward control values.

Heart rate in patients receiving halothane increased with induction of anesthesia but did not increase further with sternotomy (table 3). After cardiopulmonary bypass, heart rate continued to increase to above both control and pre-bypass levels. The heart rate values in patients receiving morphine were similar except that the increase did not occur during induction.

Patients anesthetized with halothane showed no change from control values in blood pressure or systemic vascular resistance except at 30 min after bypass, when systemic vascular resistance decreased while blood pressure remained unchanged (table 4). Patients anesthetized with morphine likewise had no change in these indices after induction, but sternotomy significantly increased both systemic vascular resistance and blood pressure. At the time of measurement, five of the six patients were receiving sodium nitroprusside (15–100 μg/min) titrated to keep systemic blood pressure within 10 per cent of control.

Patients receiving halothane showed no change in tension–time index or rate–pressure product with induction of anesthesia or sternotomy (table 5). Thirty minutes after cardiopulmonary bypass, both indices

of myocardial oxygen demand were increased, but they had begun to return toward control levels 60 min after bypass. The DPTI/TTI ratio was significantly lower than the control ratio at all times. No significant change in the ST segment of the V_5 electrocardiogram lead occurred (fig. 1). The pattern in patients receiving morphine differed. While no changes occurred with induction of anesthesia, significant increases in rate–pressure product and tension–time index occurred after sternotomy, in addition to significant ST-segment depression in the V_5 EKG lead. DPTI/TTI was decreased at all times after incision and statistically significantly decreased after sternotomy, compared with the DPTI/TTI for patients receiving halothane.

Discussion

Recognition of inadequate myocardial oxygenation is particularly difficult during general anesthesia because angina pectoris, perhaps the most reliable indicator of myocardial ischemia, cannot be expressed. Therefore, other indices must be used to assess the adequacy of myocardial oxygenation. ST-segment changes in the electrocardiogram are widely used for objective evidence of myocardial ischemia, and the use of the V_5 lead,[14] as well as inferior leads,[15] has proved of great benefit during general anesthesia. From experimental data with epicardial EKG mapping and induced epicardial ischemia, it is evident that

TABLE 3. Changes in Heart Rate

	Heart Rate (/min)				
	Awake	10 Minutes after Intubation	5 Minutes after Sternotomy	30 Minutes after Cardiopulmonary Bypass	60 Minutes after Cardiopulmonary Bypass
Morphine	62 ± 6	62 ± 3	83 ± 10*	99 ± 4*	93 ± 7*
Halothane	62 ± 4	78 ± 7*	75 ± 8	95 ± 3*	96 ± 2*

* Significant difference from awake control value, $P < .05$.

TABLE 4. Indices Reflecting Afterload

	Awake Control	10 Minutes after Intubation	5 Minutes after Sternotomy	30 Minutes after Bypass	60 Minutes after Bypass
Mean blood pressure (torr)					
Morphine	89 ± 3	89 ± 4	99 ± 2†*	83 ± 3†	89 ± 3
Halothane	99 ± 7	91 ± 8	93 ± 3	94 ± 2	95 ± 5
Systemic vascular resistance (dynes/cm/sec^{-5})					
Morphine	1,258 ± 38	1,300 ± 77	1,724 ± 183*	1,132 ± 103	1,334 ± 112
Halothane	1,347 ± 126	1,431 ± 273	1,516 ± 132	1,090 ± 105*	1,359 ± 203

* Significant difference from control, $P < .05$.
† Significant difference between anesthetic agents, $P < .05$.

TABLE 5. Indices of Oxygen Demand

	Awake Control	10 Minutes after Intubation	5 Minutes after Sternotomy	30 Minutes after Bypass	60 Minutes after Bypass
Tension–time index (torr/sec/min) × 10^{-2}					
Morphine	23.6 ± .6	24.0 ± 1.6	35.0 ± 4.4†*	24.6 ± 1.8	26.6 ± 1.0†*
Halothane	24.6 ± .8	24.4 ± 2.2	25.6 ± 2.8	31.0 ± 1.6†*	23.2 ± 1.2
Rate–pressure product (×10^{-3})					
Morphine	8.3 ± .9	7.9 ± .4	11.8 ± 1.5*	11.6 ± .8*	11.6 ± .8*
Halothane	9.0 ± .8	9.9 ± 1.4	10.4 ± 1.3	11.9 ± .9*	11.3 ± .7*
Diastolic perfusion time index/tension–time index ratio					
Morphine	.98 ± .10	.86 ± .13	.60 ± .08†*	.58 ± .07*	.61 ± .03†*
Halothane	1.12 ± .08	.79 ± .09*	.89 ± .10*	.58 ± .10*	.80 ± .10*

* Significant difference from control, $P < .05$.
† Significant difference between anesthetic agents, $P < .05$.

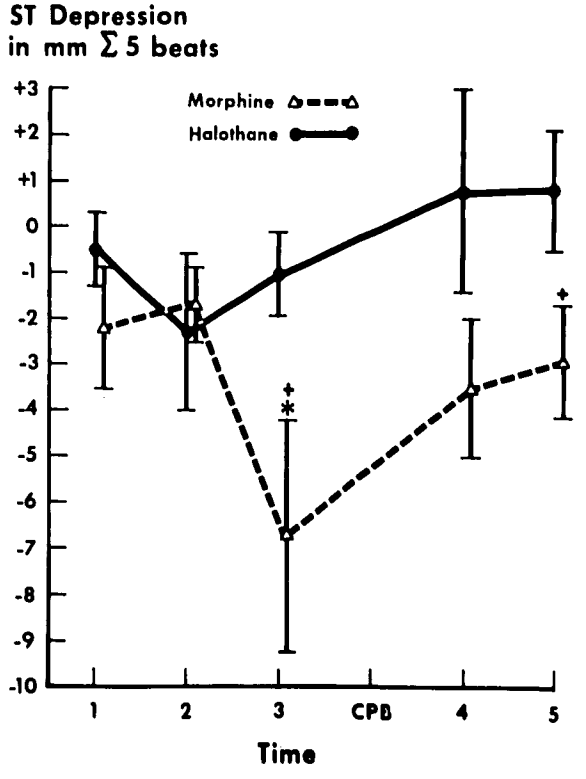

FIG. 1. Millimeters of ST-segment depression for five consecutive beats as measured in the V_5 EKG lead. C = awake control; 1 = intubated; 2 = sternotomy; CPB = cardiopulmonary bypass; 3 and 4 = 30 and 60 minutes after CPB, respectively. *Significant difference from control, $P < .05$. †Significant difference between anesthetic agents, $P < .05$.

while no consistent linear relationship exists between coronary blood flow and the extent of ST-segment change,[16] there is a good correlation between the severity and extent of ST elevation and the amount of muscle damage. Interpretation of ST-segment changes occurring with endocardial ischemia is less well defined. Nevertheless, during graded exercise tests, the amount and extent of ST-segment depression correlated with the severity of angiographically demonstrated coronary-artery obstruction and with prognosis.[17,18] Therefore, it seems reasonable to ascribe significance to the directional changes in the ST segment observed in this study.

Since patients with ischemic heart disease have impaired ability to increase the oxygen supply to the heart by increasing blood flow, prevention of ischemia and infarction are largely dependent on limiting myocardial oxygen demand. Myocardial oxygen demand is predominantly determined by ventricular wall tension, heart rate, and the level of myocardial contractility.[19] By analyzing these primary determinants of myocardial oxygen demand, one should be able to identify directional increases in oxygen demand that represent times of potential ischemia. The heart rate is easily measured. Since left ventricular wall tension is a function of left ventricular pressure and volume, directional changes in wall tension can be implied from changes in the PCW and the systemic arterial pressure. Contractility is difficult to quantify, especially in a clinical setting. Systolic time intervals, especially PEP/LVET and $1/PEP^2$, are convenient noninvasive measures of contractility but are clearly load-dependent,[11] as are cardiac index, stroke volume index, and left ventricular stroke work index. Fortunately, during a given period, preload and afterload are often not greatly altered, and assessment of directional changes in myocardial contractility using these indices is possible.

Several indices that incorporate some of the determinants of myocardial oxygen demand have become popular, including rate–pressure product and tension–time index. Studies in healthy volunteers have shown myocardial oxygen consumption correlates well with these two indices,[20] as well as with mean blood pressure, heart rate, and systemic vascular resistance.

The DPTI/TTI ratio, also called the endocardial viability ratio, includes not only the tension–time index as an index of oxygen demand but also the diastolic perfusion time index as a measure of oxygen supply. While its reliability in many circumstances is documented,[21] it has limitations. The numerator, the diastolic perfusion time index, may not be as reliable in the presence of high-grade arterial obstruction because the relationship between pressure and flow is not linear; further, the denominator, the tension–time index, is known to reflect changes in myocardial contractility poorly. Understanding their limitations, these indices remain useful clinically to help in recognition of periods of potential myocardial ischemia so that therapeutic interventions may be initiated.

There are currently many anesthetic techniques in use for aortocoronary bypass grafting. While specific details differ, the two most popular techniques are the primary use of a potent inhalational agent (halothane or enflurane) with or without nitrous oxide, and a morphine technique with adjuncts for sedation, amnesia, and control of hypertension and tachycardia. It has been demonstrated that myocardial injury, as shown by the release of a myocardium-specific creatine phosphokinase isoenzyme, often occurs before cardiopulmonary bypass, and the suggestion has been made that careful anesthetic management may decrease its incidence.[22] In an attempt to compare these two anesthetic approaches, we selected representative examples of these two techniques and observed several indices of myocardial oxygenation. Recognizing that hypertension and tachycardia are detrimental to the

patient who has coronary-artery disease, we attempted to control heart rate, preload, and afterload in patients receiving either anesthetic agent.

In agreement with previously published information, we found that hemodynamic variables were generally unchanged after induction of anesthesia in patients receiving morphine.[23] However, although average group values were unchanged, two of six patients did experience increases in PCW of more than 5 torr, and both had slight ST-segment depression and decreases in DPTI/TTI. Induction of anesthesia using halothane resulted in more varied hemodynamic changes. Some changes, such as decreased contractility, should be beneficial, but the observed increases in heart rate and PCW would be expected to increase myocardial oxygen consumption. While the mean values for DPTI/TTI and ST segments were not statistically worse, two patients given this anesthetic also showed minor (less than .5 mm) ST-segment depression. It was a clinical impression that the addition of some narcotic drug might have made induction easier and decreased the amount of halothane necessary to achieve adequate anesthesia for laryngoscopy and intubation.

The changes observed after sternotomy were somewhat unexpected. Patients receiving halothane showed no change in PCW, blood pressure, heart rate, or ST segment. In contrast, patients anesthetized with morphine had increases in heart rate, blood pressure, rate–pressure product, and tension–time index. Although as a group the PCW was unchanged, in two of six patients increases of more than 5 torr were seen. The resultant increase in myocardial oxygen consumption is reflected by statistically significant ST-segment depression and a decrease in DPTI/TTI compared with patients receiving halothane. These changes occurred despite the fact that we were using nitroprusside to minimize the hypertension often seen in patients anesthetized primarily with morphine.[9] The end results of this relatively ischemic period are difficult to assess. We did not measure myocardial creatine phosphokinase. Because the mortality rate associated with coronary-artery revascularization is about 2 per cent and the myocardial infarction rate about 10 per cent in our institution, very large numbers of patients would be needed to demonstrate differences in outcome due to choice of anesthetic agent.

The lack of myocardial depression after discontinuation of cardiopulmonary bypass in patients receiving halothane is partly an artifact of the anesthetic technique. Halothane was discontinued 5–10 min before termination of cardiopulmonary bypass and was not resumed until hemodynamic stability was achieved after termination of cardiopulmonary bypass. While "light anesthesia" with sympathetic stimulation may explain the increased myocardial contractility found during this period in patients receiving halothane, the response did not seem related to circulating catecholamines, since plasma norepinephrine and epinephrine levels in these patients were similar regardless of the anesthetic used (unpublished data). The end result of this "hyperdynamic" period is difficult to determine. Although a decrease in the DPTI/TTI ratio was observed, there was no change in the ST segments, perhaps because of an improved oxygen supply following successful revascularization. This period seems undesirable, and better baseline analgesia would be helpful. While Lappas *et al.* found no decrease in left ventricular function after cardiopulmonary bypass in patients receiving morphine,[23] we did find some myocardial depression, which abated with time. The differences may relate to methods of myocardial preservation, surgical technique, or timing of measurements.

The clinical implications of these results are intriguing, and are probably relevant not only to the relatively small group of patients undergoing coronary-artery revascularization but also to the large number of patients with coronary-artery disease undergoing general anesthesia. Clearly the choice of anesthetic agent is only one component in protecting these patients from myocardial ischemia. Understanding the patient's pathophysiologic condition, careful planning, and attention to anesthetic techniques are always of primary importance. In addition, many ancillary drugs are available to the anesthetist. Perhaps our results would have been different had we used nitroglycerin, phentolamine, propranolol, or chlorpromazine to treat hypertension. However, our selection of nitroprusside seems reasonable, since data to suggest the superiority of one drug over another are scant and often controversial.[24–26] It remains to be shown that substitution or addition of other ancillary drugs would have modified our finding of relative myocardial ischemia after sternotomy in patients anesthetized with morphine, which occurred in spite of blood pressure control to maintain levels within 10 per cent of preoperative levels.

We have found that patients undergoing coronary-artery revascularization without severe ventricular dysfunction have fewer signs of relative ischemia in the critical pre-bypass period when halothane rather than morphine anesthesia is used. It seemed somewhat more difficult to maintain PCW, heart rate, and blood pressure at control levels during induction of anesthesia with halothane, but thereafter no problem secondary to halothane-induced myocardial depression was seen. Indeed, the controlled myocardial de-

pression may have contributed to the lack of relative ischemia. Our results lead us to agree with others[1,2,6] that "light anesthesia" for patients who have coronary-artery disease without severe ventricular dysfunction is not the best anesthesia. Rather, controlled myocardial depression through the use of a potent agent such as halothane has an important role in the anesthetic management of such patients.

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