

Does Choice of Anesthetic Agent Significantly Affect Outcome after Coronary Artery Surgery?

Kenneth J. Tuman, M.D., F.C.C.P.,* Robert J. McCarthy, Pharm.D.,* Bruce D. Spiess, M.D.,*
Michael DaValle, M.D.,† Reza Dabir, M.D.,‡ Anthony D. Ivankovich, M.D.§

A prospective study of 1094 consecutive adult patients undergoing coronary revascularization was undertaken to determine the effect of anesthetic technique on outcome. Patients received one of five primary techniques: high-dose fentanyl (>50 µg/kg), moderate-dose fentanyl (<50 µg/kg), sufentanil (3-8 µg/kg), diazepam (0.4-1 mg/kg) with ketamine (3-6 mg/kg) or halothane (0.5-2.5% inspired concentration after thiopental induction). Supplemental inhalation anesthesia (enflurane, halothane, or isoflurane) was used in 60% of cases where the primary technique was intravenous based. Patients in the above anesthetic groupings had similar perioperative demographic and risk classifications. The overall incidence of postoperative myocardial infarction, postoperative low cardiac output state, and in-hospital death were 4.1, 5.6, and 3.1%, respectively. There were no significant differences in the incidence of these occurrences or in the incidence of serious pulmonary, renal, or neurologic morbidity or length of ICU stay among primary anesthetic techniques nor among supplemental inhalation agent groups. Multivariate discriminant analysis of this data suggests that a multitude of factors are significantly more important than anesthetic technique as determinants of outcome after coronary artery surgery. (Key words: Anesthesia, cardiac; outcome. Anesthetics, intravenous: diazepam; fentanyl; ketamine; sufentanil. Anesthetics, volatile: enflurane; halothane; isoflurane. Surgery: CABG; postoperative outcome.)

ANESTHETIC AGENTS directly affect the circulation as well as modify the cardiovascular responses to surgery. In addition, the actions of anesthetics are influenced by cardiovascular and general physical status, age, and adjuvant drugs. Taking these factors into account, anesthetic techniques for cardiovascular surgery are usually based on considerations such as hemodynamic stability, effects on the balance between myocardial oxygen supply and

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* Assistant Professor, Anesthesiology.

† Assistant Professor, Cardiothoracic Surgery.

‡ Fellow, Cardiothoracic Surgery.

§ Professor and Chairman, Anesthesiology.

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Address reprint requests to Dr. Tuman: Department of Anesthesiology, Rush-Presbyterian-St. Luke's Medical Center, 1753 W. Congress Parkway, Chicago, Illinois 60612.

demand,^{1,2} and minimization of perioperative stress.^{3,4} Proponents of specific anesthetic techniques for coronary artery surgery usually base their arguments on consideration of these factors.¶ As each anesthetic technique has been developed, it has been touted to be the "best" one for patients undergoing coronary artery revascularization.¹ Nonetheless, there are no current prospective studies that justify the belief that any intravenous or inhalational agent is superior in effect on outcome when used for cardiac anesthesia. The only previous prospective study of outcome in patients undergoing cardiac surgery revealed no difference in mortality in patients anesthetized with halothane compared with those anesthetized with morphine.⁵ In the 15 yr since that study, there have been significant advances in cardiac surgical practice, preoperative medical management, and knowledge and skill in managing patients during anesthesia. New monitoring techniques and new intravenous and inhalational agents have been introduced. In view of this, we examined the influence of some of these newer anesthetic agents on outcome following coronary artery surgery.

Materials and Methods

STUDY PROTOCOL

This study was approved by the institutional Human Investigation Committee. One thousand and ninety-four consecutive adult patients of seven surgeons underwent elective coronary revascularization over a 24-month period and were prospectively studied after informed consent was obtained. Nine attending anesthesiologists participated in the study as part of their regular clinical duties. Operating room assignment was based on rotation among all cardiac operating rooms, and assignment of an anesthesiologist to a patient included in this study was by chance alone.

Preoperative patient demographics and risk factors associated with a greater mortality and morbidity after cardiac surgery⁶⁻⁹ were selected for examination (table 1). Left ventricular dysfunction was defined by an ejection fraction of less than 0.3 or by a left ventricular end-dia-

¶ Bovill JG: Opioids are preferable to volatile anesthetic drugs for coronary artery surgery. *J Cardiothorac Anesth* 1:80-83, 1987; Kates RA. Volatile anesthetic drugs are preferable to opioids for coronary artery surgery. *J Cardiothorac Anesth* 1:84-86, 1987

TABLE 1. Perioperative Patient Characteristics*

	Primary Anesthetic					Anesthetic Supplement				Overall
	HDF	MDF	SUF	DK	HAL	NONE	H	E	I	
Total # of Cases	240	345	212	250	47	419	163	262	203	1094
NYHA Class II (%)	0.4	0.6	0.0	0.8	2.1	0.2	0.6	0.4	1.0	0.6
NYHA Class III (%)	30.8	29.9	34.9	32.4	23.4	33.9	30.7	35.1	23.6	31.4
NYHA Class IV (%)	68.8	69.5	65.1	66.8	74.5	65.9	68.7	64.5	75.4	68.0
Left main disease (%)	3.3	3.5	5.2	6.0	8.5	4.1	4.9	3.4	5.9	4.6
Unstable angina (%)	69.2	69.9	67.5	72.4	74.5	68.3	70.6	69.5	72.9	70.0
LV dysfunction (%)	60.4	64.9	55.2†	69.2	68.1	59.7	69.3	62.6	65.0	63.2
CHF (%)	17.1	20.6	16.5	21.2	10.6	20.3	22.7	13.0‡	21.7	18.7
Dysrhythmias (%)	29.6	31.9	27.4	30.0	36.2	28.4	29.4	29.4	34.5	30.3
MI < 6 weeks (%)	23.8	19.1	24.5	21.2	14.9	21.5	19.0	20.2	26.6	21.5
Internal mammary graft (%)	30.5	27.4	31.9	31.6	21.3	28.1	28.6	33.9	30.0	29.6
Ca entry blocking drugs (%)	75.0	74.5	70.3	67.6	76.6	69.5	79.8	74.0	69.0	72.3
β-adrenergic blocking drugs (%)	31.7	29.6	32.5	34.8	34.0	34.4	36.8	29.4	28.6	32.0
Nitrates (%)	69.2	70.4	65.1	63.6	72.3	66.6	73.0	66.4	66.0	67.6
Antihypertensive drugs (%)	26.3	24.1	19.8	20.4	19.1	22.7	21.5	22.5	24.6	22.7
Diabetes mellitus (%)	27.9	22.9	23.6	29.2	23.4	24.6	26.3	26.3	26.6	25.6
Reoperation (%)	9.6	13.9	10.8	16.0	10.6	11.7	12.3	11.5	17.2	12.7
Renal dysfunction (%)	19.6	21.7	17.9	20.4	25.5	17.9	19.0	19.5	26.6	20.4
Obesity (%)	4.2	6.1	3.3	8.0	6.4	4.3	6.1	6.1	6.9	5.6
Gender—(% male)	68.8	74.5	74.5	80.0	68.1	72.6	79.1	75.6	73.4	74.2
Age (yr)§	61.7 (10.3)	63.1 (10.2)	62.5 (9.5)	62.8 (9.9)	62.7 (11.3)	63.0 (9.7)	61.7 (10.7)‡	61.4 (10.2)‡	64.2 (9.8)	62.6 (10.1)
# of vessels grafted§	2.83 (.82)	2.82 (.92)	2.73 (.88)	2.81 (.85)	2.72 (.85)	2.82 (.84)	2.78 (.84)	2.82 (.91)	2.75 (.91)	2.80 (.87)
Cross-clamp time (min)§	70.5 (18.3)	69.8 (22.1)	68.2 (20.5)	65.3 (19.7)	68.5 (17.7)	67.8 (20.8)	68.9 (17.1)	69.5 (23.9)	70.5 (24.0)	68.5 (20.8)
MHI risk class										
Normal (%)	3.8	1.7	2.8	0.8	0.0	1.4	3.1	2.3	3.0	2.1
Increased (%)	15.0	14.5	16.0	9.6	10.6	15.3	12.9	14.9	9.9	13.6
High (%)	81.2	83.8	81.2	89.6	89.4	83.3	84.0	82.8	87.1	84.3

HDF = high-dose fentanyl; MDF = moderate-dose fentanyl; SUF = sufentanil; DK = diazepam/ketamine; HAL = halothane as primary agent; H = halothane as supplement; E = enflurane as supplement; I = isoflurane as supplement; MHI = Montreal Heart Institute Risk Classification Index.

* See text for definitions.

† $P < 0.05$ compared with other primary anesthetic techniques.

‡ $P < 0.05$ compared with other anesthetic supplements.

§ Values are means \pm SD.

stolic pressure greater than 18 mmHg at catheterization. The presence of a recent transmural myocardial infarction (less than 6 weeks) or unstable angina defined as crescendo angina during the month prior to surgery, persistent angina despite intravenous dilator therapy, and nocturnal or rest anginal pains were noted. Evidence of congestive heart failure (defined as classic chest radiograph changes in conjunction with either rales on lung auscultation or an S3 gallop on cardiac auscultation), age over 65 yr, and reoperation were noted. Obesity was considered severe enough to be a major risk factor when the Body Mass Index (weight/height²) was greater than 30 kg/m².¹⁰ Various other systemic disturbances (renal dysfunction defined as a preoperative creatinine greater than 1.4 mg/dl, dysrhythmias requiring treatment preoperatively, insulin dependent diabetes mellitus, etc.) were also noted.

From the above risk factors, the Montreal Heart Institute Risk Classification Index (MHI) was calculated.¹⁰ This index has been shown to be a reliable and useful tool for preoperative assessment of patients undergoing

cardiac surgical procedures. The preoperative risk evaluation of each patient was performed prospectively at the time of the preoperative visit. Other perioperative factors that were evaluated included absolute age, significant left main coronary artery disease (greater than 50% stenosis), type of preoperative medications (beta-adrenergic blocking drugs, calcium entry blocking drugs, nitrates, anti-hypertensive drugs), New York Heart Association functional status, gender, ischemic aortic cross-clamp time, and number of coronary revascularizations performed.

All operations were performed with a bubble oxygenator utilizing moderate hypothermia, hemodilution, and cold cardioplegic solution. Drugs used for anesthetic premedication, induction, and maintenance depended on the patients' condition, surgical requirements, and anesthesiologists' preference. Premedication consisted of various combinations of a benzodiazepene, narcotic, and scopolamine. Chronically administered beta-adrenergic blocking drugs, calcium entry blocking drugs, and nitrates were administered on the morning of operation. The anesthetic

techniques were divided among five different primary agents: high-dose fentanyl (HDF, greater than 50 $\mu\text{g}/\text{kg}$, total dose), moderate-dose fentanyl (MDF, less than 50 $\mu\text{g}/\text{kg}$, total dose), sufentanil (SUF, 3–8 $\mu\text{g}/\text{kg}$, total dose), diazepam-ketamine (DK, 0.4–1.0 mg/kg diazepam with 3–6 mg/kg ketamine, total dose), or halothane (HAL, 0.5–2.5% inspired concentration after thiopental induction). Supplemental volatile agents used included isoflurane (I), enflurane (E), and halothane (H). Neither anesthetic nor surgical techniques changed over the 24-month study period.

During the entire study period, all patients were managed depending on the patient's preoperative status and according to the usual dictates of good anesthetic care with provisions for patient amnesia, muscle relaxation, hemodynamic stability, and optimal pulmonary function. All patients had ECG monitoring of lead II and V₅ as well as intraarterial catheters for arterial pressure measurements and analysis of blood gas tensions, hematocrit, and glucose. All patients had central venous catheters and 49.1% of the patients had thermistor-tipped flow directed pulmonary artery catheters inserted in the operating room to measure pulmonary artery systolic and diastolic pressures continuously and pulmonary artery occlusion pressure intermittently. A pulmonary artery catheter was inserted at the anesthesiologist's discretion. This resulted in the use of pulmonary artery catheters in 52.5%, 60.0, 50.5, 34.0, and 25.5% of the HDF, MDF, SUF, DK, and HAL patients ($P < 0.05$), respectively, and in 44.8, 52.3, and 55.7% of the H, E, and I patients, respectively (NS). During the perioperative period, hemodynamic variables were monitored closely and hemodynamic aberrations exceeding 20% of baseline, serious dysrhythmias, and ischemia were treated pharmacologically. All patients received postoperative intensive care following standardized protocols. Postoperative hemodynamic variables, arterial blood gas tensions, electrolytes, hemoglobin, and urine output were monitored closely under the direction of a staff surgeon, cardiologist, and anesthesiologist trained in critical care. All postoperative care was rendered by personnel who were unaware of the goals of the study.

At any time before or after cardiopulmonary bypass and throughout the ICU period, if systemic arterial blood pressure or cardiac output were deemed inadequate (*e.g.*, by noting the presence of oliguria, an otherwise unexplained base deficit, desaturation of mixed venous hemoglobin, etc.), corrective measures were taken. In general, fluid was administered if the right atrial pressure (or pulmonary artery occlusion pressure if available) was less than preoperative values. After cardiopulmonary bypass, blood was transfused if hemoglobin levels fell below 9 g/dl. If RAP (or PAOP) equalled or exceeded the preoperative values, vasoactive infusions were administered. The choice of vasoactive infusion depended on the he-

modynamic profile obtained if a pulmonary artery catheter was present, clinical circumstance, and physician preference. Vasoactive infusions included dopamine, dobutamine, amrinone, epinephrine, and isoproterenol (in patients without ischemic heart disease). If, despite adequate anesthesia intraoperatively, or at any time postoperatively, systemic vasodilators were needed, either nitroglycerin or nitroprusside were used, depending on clinical circumstance and physician preference. Intra-aortic balloon counterpulsation was employed whenever perfusion was inadequate, despite pharmacologic and fluid treatment of preload, afterload, and contractile conditions.

All patients remained in the ICU for at least the first 2 postoperative days, regardless of clinical status. Thereafter, ICU discharge was determined by surgical staff and depended on their assessment of overall patient course and cardiopulmonary stability. In general, since a "step-down" unit is not employed at our institution, patients were transferred from the ICU to a regular hospital bed only after they were free from requiring vasoactive infusions, invasive monitoring, fluid administration above maintenance levels, or aggressive pulmonary therapy for at least 24 h.

Perioperative hemodynamic aberrations such as hypertension or hypotension requiring vasoactive infusions, low cardiac output syndrome (requiring an intraaortic counterpulsation device), serious dysrhythmias (defined as frequent premature ventricular beats requiring treatment, ventricular tachycardia or fibrillation, supraventricular tachydysrhythmias which required treatment due to concomitant evidence of myocardial ischemia, hypotension or a rapid ventricular response, or heart block requiring the use of pacing), and ECG evidence of ischemia defined as a greater than 0.1 mV or more of positive or negative horizontal ST segment shift, which extended at least 80 msec beyond the J point of the QRS complex in any ECG lead, were noted through the duration of the ICU stay. Hard copies of lead II or V₅ were obtained every 4 h in the ICU and more frequently if changes suggestive of ischemia (ST segment or T wave abnormalities) or dysrhythmias were noted on continuous oscillographic displays. In the postoperative period, serial hard-copy 12-lead ECG and creatine kinase MB isoenzyme (CK-MB) studies were done on arrival in the ICU and daily for the initial 3 postoperative days and then every third day until hospital discharge. All hard copy ECG recordings were calibrated using a 1 mV standard. Appearance of new and persistent Q waves of greater than 0.04 s in duration and 1 mm or more in depth in the absence of bundle branch blocks or major QRS axis changes in the postoperative ECG and significant increase in cardiac specific enzymes (CK-MB greater than 80 IU/liter) were considered as positive evidence of postoperative myocardial infarction (PMI). Serious pulmonary compli-

cations were defined as the need for prolonged tracheal intubation (greater than 24 h postoperatively) or for reintubation and mechanical ventilation, hypoxemia, severe bronchospasm, or acute lung injury (ARDS). Renal insufficiency was defined as a postoperative increase in serum creatinine of more than 2 mg/dl. Postoperative neurologic abnormalities were considered present when sensory, motor, or reflex abnormalities were found at any time after ICU entry or if global abnormalities (with or without focal signs) such as combativeness, disorientation, hallucinations, stupor, or coma were noted within 2 days of surgery. Overall mortality (OM) was defined as death that occurred after the operation was commenced and before discharge from the hospital. Mortality was divided into deaths that occurred in the operating room during the original procedure and those that occurred postoperatively.

DATA ANALYSIS

Data were collected by a full-time data manager and were stored and analyzed on an Intel® 80386 based microcomputer. Patient demographics and perioperative risk factors, as well as the incidence of postcardiopulmonary bypass morbidity and mortality among anesthetic groups, were compared. Two-way analysis of variance was used to compare data for age, ischemic cross-clamp time, number of vessels revascularized, and length of ICU stay among anesthesia groups. When appropriate, secondary tests were performed using the Tukey-a method. The Chi-square test was used to compare all other data between groups. The null hypothesis was rejected when *P* was less than 0.05.

Discriminant analysis was used to develop a rule to distinguish between those who had and those who did not have PMI after coronary revascularization procedures, as well as those who survived and those who did not survive. The first step in this process was the examination of variables that measure characteristics that were expected to differ in the two groups. Twenty-four independent historical, physical, and laboratory variables were tested individually for their univariate relationship to the dependent variables (OM and PMI). Multivariate discriminant analysis was then used to select the linear combination of variables that separate survivors from nonsurvivors, as well as those with PMI from those without. The process was carried out in a stepwise manner utilizing the minimum Wilks' lambda as a measure of group discrimination. At each step in the process, the variable that contained the most discriminating power, when added to the variables already selected for the model, was identified. The process was stopped when the remaining (nonselected) variables all had additional discriminating ability that did not further reduce Wilks' lambda by at least 0.001. In

building this model, the discriminant analysis takes account of the relationships among the variables and corrects for covariates containing redundant information at each step of the analysis. The multivariate determinants were ranked according to their *F* statistics to indicate relative statistical predictive power. The relative weighting of each variable included in the predictive model is designated by the canonical discriminant coefficient, the sign of which depicts whether there is a direct or inverse relation to the dependent variable (OM or PMI). Thus, multivariate discriminant analysis was used to compare the relative importance of anesthetic technique to other factors influencing the major outcome events of OM and PMI. From the factors that remained significantly related after discriminant analysis, a classification table was created that utilized the discriminant function to test its predictive strength. Predictive accuracy of the discriminant function was assessed by comparing actual to predicted outcomes at various levels of discriminant function score.

Results

PATIENT POPULATION

Of the 1094 adult patients who underwent coronary artery surgery, 240 received HDF, 345 MDF, 212 SUF, 250 DK, and 47 HAL as their primary anesthetic agent. Of the 1047 patients receiving primarily intravenous techniques, 60% received supplemental volatile agents. 203 patients received supplementation with isoflurane, 262 with enflurane, and 163 with halothane. The preoperative assessment and characteristics of the patients are presented in table 1. The study groups are comparable based on these criteria with a few minor differences. There were no differences among the primary anesthetic techniques for any of the 21 perioperative patient characteristics except for a lower incidence of ventricular dysfunction in the SUF group than the other primary anesthetic techniques. The only significant differences among patients receiving supplemental volatile anesthetic agents were a lower incidence of preoperative CHF among enflurane patients and a tendency for halothane and enflurane patients to be approximately 2 yr younger than patients receiving isoflurane or no volatile agent.

PERIOPERATIVE COMPLICATIONS AND OUTCOME

As shown in table 2, there was no significant difference in the incidence of serious dysrhythmias, tachycardia, low cardiac output requiring IABP, pulmonary or neurologic complications, or renal dysfunction among groups of patients receiving the different anesthetic agents. The only outcome characteristic that differed significantly among anesthesia groups were a lower incidence of ECG evidence

TABLE 2. Postcardiopulmonary Bypass Morbidity and Mortality

	Primary Anesthetic					Anesthetic Supplement				Overall
	HDF	MDF	SUF	DK	HAL	NONE	H	E	I	
Mortality										
Intraoperative (%)	1.7	1.4	0.9	0.0	0.0	1.4	1.2	1.1	0.0	1.0
Postoperative (%)	2.9	1.8	1.9	1.6	4.3	2.2	2.5	2.0	1.5	2.1
Overall (%)	4.6	3.2	2.8	1.6	4.3	3.6	3.7	3.1	1.5	3.1
Morbidity*										
HR > 110 bpm (%)	11.0	10.9	16.7	14.0	8.5	13.8	13.7	12.0	11.3	12.7
ECG changes (%)	20.8	26.8	24.3	13.2‡	31.9	19.1	22.4	22.4	25.1	22.1
Postop MI (%)	4.7	4.4	4.3	2.8	4.3	4.4	4.3	4.2	3.0	4.1
Serious dysrhythmias (%)	25.4	21.5	19.0	21.2	31.9	19.6	28.6	20.1	23.2	22.3
Use of vasodilators (%)	14.0	17.6	21.4	22.0	19.1	15.7	25.5	19.3	18.2	18.7
Use of vasopressors (%)	22.0	21.2	19.5	9.6‡	21.3	17.2	23.6	15.4	19.7	18.4
Postoperative IABP (%)	6.4	7.1	5.2	3.6	2.2	4.9	4.4	6.1	7.4	5.6
Pulmonary Morbidity (%)	7.2	9.7	6.2	6.4	10.6	8.1	6.4	8.2	7.7	7.8
Renal dysfunction (%)	5.5	2.6	3.8	3.6	8.5	3.4	4.3	3.5	5.4	4.0
Neurologic event (%)	4.2	5.3	5.7	2.0	0.0	4.8	5.3	3.1	3.0	4.2
ICU days†	3.25 (2.12)	3.31 (2.97)	2.97 (2.34)	3.07 (2.14)	3.02 (0.51)	3.14 (2.19)	3.12 (2.81)	3.31 (2.97)	3.08 (1.49)	3.16 (2.41)

Abbreviations as in table 1.
* See text for definitions.

† Values are means (± SD).
‡ P < 0.05 compared to other primary anesthetics.

of ischemia and a lower incidence of hypotension requiring treatment with vasopressor in patients who received diazepam-ketamine. The incidence of hypertension requiring intravenous vasodilator treatment was not different among groups. Endpoints of clinical outcome were judged by incidence of mortality, postoperative myocardial infarction, and length of ICU stay. There was an even distribution of the latter parameters among the anesthesia groups (table 2).

DETERMINANTS OF OPERATIVE RISK

The 24 variables used in the univariate and subsequent multivariate discriminant analysis are those listed in tables 3 and 4. For the entire patient population, univariate analysis showed that prolonged aortic cross clamp time, recent MI, CHF, serious preoperative dysrhythmias, and higher NYHA functional class all correlated with higher mortality rates (table 3). The remainder of the variables, including surgeon, anesthesiologist, anesthetic agent, and use of a PA catheter were not significantly related to overall mortality in the univariate analysis. In the multivariate analysis, prolonged aortic cross clamp time was the strongest determinant of overall mortality rate, followed by recent MI, preoperative CHF, inability to use an internal mammary artery graft, serious preoperative dysrhythmias, left main disease, higher NYHA functional class, and unstable angina.

Univariate analysis showed that recent MI, prolonged aortic cross clamp time, non-use of calcium entry blocking

drugs, and serious preoperative dysrhythmias all correlated with higher incidence of PMI (table 4). Recent MI was the strongest significant multivariate predictor of PMI. Prolonged aortic cross clamp time, non-use of calcium entry and beta-adrenergic blocking drugs, preoperative CHF and serious dysrhythmias, and female gender were weaker but significant determinants of PMI. Thus, prolonged cross clamp times, recent MI, serious preoperative dysrhythmias, and CHF were significant multivariate determinants of both PMI and OM, although the remainder of the significant multivariate determinants of these respective outcomes differed (tables 3, 4).

Univariate statistical methods failed to demonstrate any significant impact of anesthetic technique on the outcome variables of OM and PMI. The findings were the same even when considering the inter-relationship of anesthetic technique with various risk factors by using multivariate discriminant analysis.

Using the discriminant functions developed, a classification table was constructed to test their predictive strength for OM and PMI at various levels of discriminant probabilities (table 5). Predictive ability of the discriminant function was best at the lowest probability levels and worst at the highest probability levels. Overall, assuming an equal probability of outcome for each patient, there were 77.9% (OM) and 73.7% (PMI) correct predictions (e.g., number of correctly predicted survivors and correctly predicted nonsurvivors/total number of cases). It must be noted that these results are based on retrospective classification of the same patients from whom the score was developed.

TABLE 3. Determinants of Overall Mortality

Variable	Univariate		Multivariate		
	F	P	Discriminant F	Analysis P value	Discriminant Coefficient
Cross-clamp time	34.66	.00001	33.35	.00001	.726
Recent MI	10.33	.001	11.18	.00001	.433
CHF	8.81	.003	3.15	.00001	.232
Internal mammary graft	2.38	.123	3.13	.00001	-.229
Serious dysrhythmias	8.61	.003	3.17	.00001	.230
Left main disease	1.46	.228	2.02	.00001	.179
NYHA class	6.95	.009	2.42	.00001	.209
Unstable angina	<1	.759	1.77	.00001	.177
LV dysfunction	2.89	.090	<1	NS	
MHI risk class	2.67	.102	<1	NS	
Anesthesiologist	2.67	.102	<1	NS	
Use of PA catheter	2.26	.133	<1	NS	
Primary anesthetic agent	2.19	.139	<1	NS	
Age	1.73	.189	<1	NS	
Use of β -adrenergic blocking drugs	1.15	.283	<1	NS	
Diabetes mellitus	<1	.359	<1	NS	
Renal dysfunction	<1	.371	<1	NS	
Reoperation	<1	.380	<1	NS	
Use of Ca entry blocking drugs	<1	.538	<1	NS	
# of vessels grafted	<1	.588	<1	NS	
Gender	<1	.622	<1	NS	
Surgeon	<1	.647	<1	NS	
Inhalation anesthetic agent	<1	.899	<1	NS	
Use of nitrates	<1	.999	<1	NS	

TABLE 4. Determinants of Postoperative MI

Variable	Univariate		Multivariate		
	F	P	Discriminant F	Analysis P value	Discriminant Coefficient
Recent MI	27.10	.00001	28.82	.00001	.705
Cross-clamp time	9.44	.002	11.02	.00001	.437
Use of Ca entry blocking drugs	7.34	.007	9.71	.00001	-.411
CHF	2.72	.099	6.30	.00001	.336
Serious dysrhythmias	6.97	.008	3.90	.00001	.266
Gender	1.58	.209	2.59	.00001	-.212
Use of β -adrenergic blocking drugs	1.86	.173	1.08	.00001	-.138
# of vessels grafted	2.43	.120	<1	NS	
Unstable angina	1.16	.282	<1	NS	
Surgeon	<1	.322	<1	NS	
Primary anesthetic agent	<1	.365	<1	NS	
LV dysfunction	<1	.389	<1	NS	
Left main disease	<1	.450	<1	NS	
NYHA class	<1	.558	<1	NS	
Age	<1	.570	<1	NS	
Use of PA catheter	<1	.634	<1	NS	
Renal dysfunction	<1	.709	<1	NS	
Internal mammary graft	<1	.747	<1	NS	
MHI risk class	<1	.755	<1	NS	
Diabetes mellitus	<1	.781	<1	NS	
Anesthesiologist	<1	.803	<1	NS	
Reoperation	<1	.811	<1	NS	
Inhalation anesthetic agent	<1	.933	<1	NS	
Use of nitrates	<1	.942	<1	NS	

Discussion

Controversy exists as to which anesthetic drug or technique should be selected for patients undergoing coronary revascularization. When used alone, opiates are unlikely to depress myocardial contractility but may fail to blunt sympathetic nervous system response to noxious stimulation with potentially deleterious effects on myocardial oxygen demand.¹¹ Volatile anesthetics blunt adverse responses to noxious stimulation but may reduce systemic blood pressure and thus coronary perfusion pressure necessary for flow past an obstructive coronary lesion.¹²⁻¹⁴ Additionally, isoflurane may act as a coronary arteriolar vasodilator and may induce coronary artery steal and regional myocardial ischemia which may or may not be due to decreases in coronary perfusion pressure.^{14,15} Although ketamine as a single agent has been criticized by some because of potential increases in myocardial oxygen demand,¹⁶ others have supported its use with benzodiazepenes by demonstrating stable intraoperative hemodynamics^{17,18**} and attenuation of the neuroendocrine stress response during adult cardiac surgery that is similar to that obtained with opiates.¹⁹ Diazepam-ketamine, as well as halothane alone, are not currently widely used as the sole maintenance agents for coronary artery surgery, and their inclusion in this study broadens the range of anesthetic techniques studied. Part of our goal in this study was to examine as broad a variety of anesthetic techniques as possible, with the belief that this would have the greatest chance of demonstrating significant differences in outcome in those patients most susceptible to adverse perioperative events. However, relatively few anesthesiologists at our institution (and nationwide) currently have experience using either diazepam-ketamine or halothane alone in patients undergoing coronary artery surgery. The feasibility of performing a truly randomized study that included these techniques was therefore constrained at our institution. A randomized comparative study that includes use of these techniques in high-risk cardiac surgical patients is not likely to be undertaken elsewhere for similar reasons. We acknowledge that the lack of true randomization may introduce an unmeasurable and unidentified bias, but believe that any unknown confounding factors are probably evenly distributed among the resulting groups of anesthetics because of the large sample size. As shown in table 1, there are no major differences in patient characteristics or risk assessment among the various anesthetic groupings. There was also no difference in the incidence of postoperative myocardial

** Tuman KJ, Keane DM, Silins AI, McCarthy RJ, Spiess BD, Ivanovich AD: Effects of high dose fentanyl on fluid and vasopressor requirements after cardiac surgery. *J Cardiothorac Anesth* 2:419-429, 1988

infarction or death among the group of anesthesiologists involved in this study.

With these caveats, how should the results of this study be interpreted? Previous publications too numerous to list have shown that anesthetic agents differ in the hemodynamic, metabolic, and other physiologic responses they produce. Therefore, one might expect that the net advantage of one technique over another, based on measurement of physiologic effects, would produce a more favorable outcome. However, simply showing that one technique produces more optimal physiologic effects (processed variables such as blood pressure, heart rate, etc.) is not sufficient to conclude that the technique improves outcome variables (postoperative myocardial infarction, death, length of ICU stay). For example, the decreased incidence of hypotension requiring vasopressors and the lower incidence of post-bypass ECG changes in patients receiving DK was not associated with any significant difference in the outcomes of PMI or OM. The latter findings are consistent with an earlier controlled study comparing the postoperative hemodynamics of diazepam-ketamine with high-dose fentanyl in 40 patients undergoing cardiac surgery.** Although several studies have shown that process variables and outcome variables can be poorly correlated,²⁰⁻²³ most recommendations about choice of anesthetics are long on opinions based on processed variables and short on outcome data. If outcome with respect to ischemic events, infarction, and death are no different among a wide variety of agents, one must question the clinical relevance of using the presence or absence of such physiologic variables as coronary sinus lactate extraction as the basis for selecting or not selecting certain anesthetic agents for coronary artery surgery.¹ Furthermore, the failure of the perioperative risk factors used in this study to accurately predict PMI (table 5) raises the question of the validity of basing anesthetic management decisions on preoperative variables such as ejection fraction, presence of CHF, or age of recent MI. Factors that correlate with postoperative hypercoagulability, graft spasm, and thrombosis might improve our ability to predict PMI, but such factors are not quantifiable at this time. Other investigators have similarly been unsuccessful in building accurate discriminant models of prediction for PMI by using preoperative patient characteristics.²⁴

The effects of anesthetics on process variables (e.g., heart rate, blood pressure, etc.) are usually studied in small groups of relatively young humans with normal ventricular function or in animals with acute or chronic ischemia limited to a single coronary artery. Thus, extrapolation of favorable outcome effects of any given technique based on favorable physiologic effects would apply at best to a select patient subset. There are few data from patients with significant ventricular dysfunction or patients with recent MI undergoing coronary revascularization. It is

TABLE 5. Actual versus Probability of Outcomes Based on Multivariate Discriminant Analysis of Perioperative Variables

	Probability of Outcome (%)	Discriminant Score	# of Patients	% Actual Outcome
Death	0-25	-2.97 to -.104	536	1.1
	25-50	-.097 to .666	308	2.3
	50-70	.671 to 1.26	142	2.8
	70-80	1.27 to 1.63	45	6.7
	80-90	1.65 to 2.21	37	16.2
PMI*	90-100	2.24 to 6.87	26	30.8
	0-25	-2.61 to -.358	411	1.2
	25-50	-.355 to .551	367	1.9
	50-70	.555 to 1.25	183	7.1
	70-80	1.26 to 1.67	62	6.5
	80-90	1.71 to 2.37	36	19.4
	90-100	2.38 to 4.21	24	33.3

* Excludes intraoperative deaths.

just these patients in whom outcome might be critically affected by perioperative events which might be modulated by anesthetic agents. The problem is compounded by the fact that patients undergoing cardiac surgery represent a very heterogeneous group of patients. On the healthy end of the spectrum, there are patients who will probably do well regardless of anesthetic agent. This is the group of patients in whom most physiologic studies of agents are performed. At the opposite end of the spectrum are patients who have such severe disease that they probably will do poorly with any technique no matter how carefully it is administered. In between these two extremes are the population of patients in which anesthetic agent might make a difference to outcome. Looking at the risk profiles of our patient population indicates that our study may be examining this category of patients (63.2% with LV dysfunction, mean age 62.6 yr with 25.1% of patients age 70 yr or older, and 84.3% high risk MHI class).

There is a growing body of data that documents a high incidence of silent ischemia due to reduction in coronary perfusion without tachycardia or changes in arterial blood pressure or pulmonary artery occlusion pressure in the perioperative period before cardiopulmonary bypass.²⁵⁻²⁷ One of these studies²⁵ showed that the incidence of reduced coronary perfusion in the absence of hemodynamic change was the same with two different anesthetic techniques. Prior studies of patients with cardiac disease undergoing noncardiac surgery have demonstrated that type of anesthetic technique does not influence the incidence of postoperative myocardial reinfarction.²⁶⁻³⁰ Because as many as one-half of all episodes of perioperative ischemia are not preventable by preserving a favorable balance between hemodynamic indices of myocardial oxygen supply and demand, it may be that the effect of anesthetics on hemodynamic factors that balance myocardial O₂ supply and demand are less important

than previously thought. Although some data suggest that anesthesia itself is beneficial to the ischemic heart by decreasing the incidence of these hemodynamically unrelated episodes,²⁷ detection and treatment of these episodes in the perioperative period are more likely to affect outcome than the specific agent used, since their occurrence is probably a manifestation of coronary artery disease completely unrelated to anesthesia and operation.

The final outcome events of postoperative myocardial infarction and death are not completely independent variables. Up to 40% of long-term deaths following cardiac surgery are related to myocardial infarction.^{31,32} Of the 34 in-hospital deaths in this study, 53% were related to cardiac causes (perioperative myocardial ischemia or infarction, malignant ventricular dysrhythmias, and pump failure that was attributed to the seriousness of the patient's disease, as well as errors in operative technique, such as excessive bleeding or thrombosis of coronary grafts). A recent national review of quality control for cardiac surgery concluded that more than 60% of deaths after cardiac surgery are due to primary errors in operative technique, operative judgment, or inadequate myocardial preservation during cardiopulmonary bypass.³³ This study reported similar mortality rates as our study and the national panel of surgeons and cardiologists who reviewed the deaths also concluded that over 70% of all deaths were multifactorial and included other factors, such as seriousness of the patient's primary disease and postoperative management problems, in addition to the technical and judgment errors involved above. In our study, 44% of the overall mortality was attributable to multifactorial causes, such as major postoperative neurologic events, sepsis, and multiple organ failure. Severe postoperative central nervous system complications were felt to be a major contributing cause in 60% of the latter cases. Previous work suggests that air or particulate emboli originating within the heart or aorta are the major causes of cerebral dysfunction³⁴ after extracorporeal circulation and that perfusion pressure correlates poorly with the development of CNS injury. None of the patients in our study who died with major postoperative CNS injury had low perfusion pressures, although most of them had cerebral vascular disease or embolic phenomena documented or suspected. Our overall incidence of neurologic complications is well within the range reported for the occurrence of neuropsychiatric complications following operations involving extracorporeal circulation (1.6% to 23%).³⁴ When considering important mediators of morbidity and mortality, it is extremely unlikely that choice of anesthetic agent *per se* would have any significant interaction with the occurrence of embolic phenomenon, errors in operative technique or judgment, or inadequate myocardial preservation during the period of interruption

of coronary blood flow. Multivariate discriminant analysis revealed that aortic cross-clamp time, which reflects not only severity of anatomic disease but surgical expertise as well, was a much more significant predictor of either PMI or OM.

Unfortunately, studying the effects of anesthesia upon outcome of patients undergoing cardiac surgery is of necessity imprecise because of the multifactorial nature of outcome determinants. As Keats has pointed out, "no control study of the hazards of operation without anesthesia or conversely anesthesia without operation will ever be performed. The hazards of anesthesia can never be considered independent of a second procedure."³⁵ This is especially likely in operations such as cardiac procedures where the procedure itself entails significant intrinsic risk. Although the potential interactions of anesthetic agents with vital organ systems, disease states, drugs, and surgical intervention are logical, they are difficult to quantitate. The results of our preliminary work suggest that these interactions may not be as important to final outcome in the setting of cardiac surgery as previously thought. Because of the above considerations, it is not likely that even a multi-center, randomized study would be able to better answer the question of whether choice of anesthetic is critical to outcome after cardiac surgery. Nonetheless, information derived from a large cooperative series might be of additional help.

Any anesthetic agent or technique may be improperly used, and no potential or actual benefit of any anesthetic technique exists without some cost or disadvantage. An anesthesiologist without the experience of using diazepam-ketamine or a single potent agent such as halothane for the primary technique in adult cardiac surgery is not likely to use it as efficaciously as someone who has been using the technique for many years. Conversely, when new techniques are introduced, their use may not be optimal until clinical experience is gained after repeated uses. For example, the early use of large doses of sufentanil was shown to produce a significant degree of hypotension when administered with benzodiazepenes to patients undergoing cardiac surgery.³⁶ Subsequent experience has made anesthesiologists aware of such a potential interaction and thus avoid such potentially adverse effects. It is perhaps because the clinician understands these potential interactions of anesthetic agents with the patient's disease, other drugs, and surgical events, and compensates for them so well that outcomes do not differ among anesthetic agents. These compensations involve adjusting dosages; adding drugs to increase or decrease heart rate, perfusion pressure, or contractility; correcting preload deficits or excesses; treating hypoxemia; maintaining adequate hemoglobin levels; and, in general, providing an optimal balance between oxygen requirements and oxy-

gen delivery in all organs, not just the heart. Avoidance of a rigid approach by choosing the combination of drugs, anesthetic and nonanesthetic, to achieve this goal is probably more important than which individual drugs are used. Perhaps we found no differences in outcome simply because intraoperative hemodynamics were tightly controlled and dysrhythmias and ischemia aggressively treated regardless of anesthetic agent.

The major limitation of this investigation was our inability to have patients randomly assigned to anesthetic agent groups. Nevertheless, among assignment groups, there was no objective evidence of major differences in severity of disease, preoperative medication, or overall risk assessment. Despite this, physician preference influenced a variety of factors, including, but not restricted to, use of anesthetic, use of pulmonary artery catheter, and the decision to use specific vasoactive drugs. Although multivariate discriminant analysis did not reveal these potential confounding effects, our data provide no basis for supporting or denying the presence of such unidentified biases.

In summary, we have demonstrated in a large series of high-risk patients undergoing coronary artery surgery that there is no significant difference in cardiac or noncardiac complications, in-hospital death, or ICU stay among a wide variety of intravenous techniques with or without inhalation supplementation, including isoflurane. Our data fail to justify the belief that any one of the intravenous or inhalational agents we studied is any more beneficial in effect on outcome when used for patients undergoing coronary revascularization. Determinants of outcome after cardiac surgery are multifactorial and appear to depend less on anesthetic agent *per se* and more on careful clinical technique (including prompt appropriate management of hemodynamic aberrations and ischemia), preoperative patient characteristics, and technical factors.

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