

Randomized Trial of Primary Anesthetic Agents on Outcome of Coronary Artery Bypass Operations

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To examine the role of primary anesthetic agent on outcome of coronary artery bypass grafting operations, 1,012 patients were prospectively randomized to receive enflurane (257), halothane (253), isoflurane (248), or sufentanil (254). Except for administration of the primary anesthetic, anesthesia management was standardized for all patients. The randomized groups did not differ in demographic characteristics, extent of coronary artery disease, chronic antianginal therapy, hemodynamic characteristics including new myocardial ischemia at arrival to the operating room, and surgical characteristics that might influence the rate of postoperative myocardial infarction or death. From anesthetic induction to start of cardiopulmonary bypass, new ST segment depression appeared in 310 (30.4%) patients and was not different among primary anesthetic groups (28.0-33.5%). Similarly, the incidence of postoperative myocardial infarction (3.6-4.7%) and death (1.2-2.4%) was not different. Although intraoperative hypotension was twice as common in patients receiving any volatile anesthetic and hypertension twice as common with sufentanil, tachycardia (≥ 110 bpm) was not related to any primary anesthetic (4.3-9.1%) and was the only hemodynamic abnormality significantly related to intraoperative ischemia. The strongest predictor of intraoperative ischemia was ischemia on arrival to the operating room. The authors postulate that approximately 90% of new myocardial ischemia observed during anesthesia is the manifestation of silent ischemia observed in patients before operation and only 10% is related to anesthetic management. They conclude that, despite differences in the hemodynamic consequences of the primary anesthetics studied, none of the primary anesthetics influenced outcome and the primary role of the anesthesiologist in management of these patients is control of heart rate. (Key words: Anesthesia; cardiovascular. Anesthetics, intravenous: sufentanil. Anesthetics, volatile: enflurane; halothane; isoflurane. Heart: infarction; ischemia. Surgery: cardiac; myocardial revascularization.)

IN THREE PREVIOUS PROSPECTIVE STUDIES¹⁻³ that included 1,962 patients undergoing coronary artery bypass grafting (CABG), we demonstrated that new myocardial

ischemia appearing between arrival to the operating room and start of cardiopulmonary bypass (CPB) was associated with increased risk of postoperative myocardial infarction (PMI). By design, in these investigations, choice of primary anesthetic agent was not controlled and varied with each anesthesiologist. Most commonly, halothane, enflurane, or isoflurane was the primary anesthetic agent and less often a high dose narcotic technique was used. Others have examined primary anesthetic agents in terms of hemodynamic changes during CABG.⁴⁻⁷ In addition, inhalation agents and narcotics have been compared for their role in the genesis of regional or global myocardial ischemia in animals and in small groups of patients with partially occluded coronary vessels.⁸⁻¹⁴ No study, however, examined the isolated effect of primary anesthetic drug on either incidence of new intraoperative ischemia or on outcome of CABG in a large patient population. We now report the results of such a study in which 1012 patients were randomized to receive one of four primary anesthetic agents with all other aspects of anesthetic management standardized. The purpose of the study was to examine the role of the primary anesthetic agent, each with its unique hemodynamic consequences, on the appearance of new myocardial ischemia during anesthesia and on the incidence of postoperative myocardial infarction and/or death.

Materials and Methods

With institutional review board approval, all patients 21-75 yr of age scheduled for elective CABG by four participating surgeons were eligible for study. Patients were excluded if any of the following obtained: previous cardiac operation, emergency operation, operations performed in addition to CABG, severe systemic noncardiac disease other than diabetes and hypertension, history of allergy to any drug that might be administered, preoperative electrocardiogram that precluded diagnosis of ischemia, such as left bundle branch block (LBBB), or failure to obtain consent. From September 1, 1985, to July 30, 1987, data relating to the perioperative experience of 1012 patients were collected prospectively representing approximately 80% of all eligible patients.

PRIMARY ANESTHETIC RANDOMIZATION

After qualifying and consenting, each patient was assigned a primary anesthetic agent. To eliminate the role

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of surgical technique in outcome, primary drug assignment was randomized for each of four surgeons from four different tables of random numbers. Except for primary anesthetic agent, all patients were managed identically. After 5 min of denitrogenation, patients to receive a volatile agent had anesthesia induced with diazepam 250–400 $\mu\text{g}/\text{kg}$, pancuronium 150 $\mu\text{g}/\text{kg}$, and fentanyl 10 $\mu\text{g}/\text{kg}$. At onset of unconsciousness, the assigned inhalation agent was introduced and maintained in sufficient concentration until blood pressure stabilized within limits defined for each patient (see below). After at least 5 min of volatile agent administration, tracheal intubation was performed when blood pressure was near the lower end of the defined limit. The inhalation agent was continued until start of CPB, except when blood pressure fell below the defined limit when it was withheld for no longer than 2 min. No other anesthetic drugs were given before CPB. Patients assigned to receive sufentanil were given pancuronium 30 $\mu\text{g}/\text{kg}$, followed by sufentanil 15–25 $\mu\text{g}/\text{kg}$ after denitrogenation. Ventilation was assisted with pure oxygen as required and, after loss of consciousness, pancuronium 120 $\mu\text{g}/\text{kg}$ was given and the trachea intubated. After skin incision but before sternotomy, an additional dose of sufentanil 5 $\mu\text{g}/\text{kg}$ was administered. No further anesthetic drugs were given before CPB. Nitrous oxide was not administered to any patient. During CPB, diazepam, thiopental, or additional narcotic could be administered at the discretion of the anesthesiologist, who could also administer the primary anesthetic drug to which the patient was randomized after CPB, if desired.

STANDARDIZED ANESTHETIC MANAGEMENT

Each patient was visited preoperatively by one of nine participating anesthesiologists and fasted overnight. Approximately 2 h before scheduled induction of anesthesia, diazepam 5–10 mg or lorazepam 2–4 mg was administered by mouth. Approximately 1 h before induction, morphine 5–10 mg or meperidine 50–100 mg, plus scopolamine 0.1 mg, were administered intramuscularly. Preoperative oral administration of chronically taken beta adrenergic blocking drugs, calcium entry blocking drugs, and oral or topical nitrates was continued on the morning of operation or deleted at the discretion of the anesthesiologist. Upon arrival to the operating room, electrocardiographic and intra-arterial blood pressure monitoring was instituted. Heart rate greater than 89 bpm with or without new myocardial ischemia and/or anginal pain was treated with intravenous propranolol 1–3 mg. In nine patients with angina on arrival to the operating room and ischemia at slow heart rates, sublingual nitroglycerin was administered. Patients with painless ischemia not related to tachycardia and patients with hypertension were not treated during the preinduction period. For each patient, mean preoperative systolic blood pressure and heart rate

were calculated by averaging from six to 20 bedside values recorded during the preoperative hospital stay. These values were available to the anesthesiologist on arrival to the operating room. For the purpose of standardizing intraoperative management and indications for treatment, hypertension was considered the greater of systolic pressure 20% above mean preoperative systolic pressure or 180 mmHg, hypotension the lower of systolic pressure 20% below mean preoperative systolic pressure or 90 mmHg, and tachycardia the lower of heart rate 20% above mean preoperative rate or 90 bpm. During the period from induction of anesthesia to onset of CPB in all patients, hypertension was treated by increasing concentration of volatile agent or nitroprusside infusion, hypotension by decreasing the concentration of volatile agent or intravenous phenylephrine or ephedrine based on heart rate and tachycardia by intravenous propranolol or, if history of bronchospasm was present, verapamil. Treatment was the same whether or not associated with ST segment deviation. In the absence of any hemodynamic abnormality, ST segment depression of at least 0.1 mV was treated by nitroglycerin 50 μg intravenously. Compliance with the protocol was examined for administration of assigned primary agent, non-use of nitrous oxide, non-use of nonprotocol drugs, completeness of patient information, and completeness of data for the entire study period. Compliance in these areas was 100%. Compliance with the treatment protocol for hemodynamic abnormalities and/or ischemic changes was examined by computer review and ranged from 70–82% for the nine anesthesiologists. All instances of non-compliance were attributable to lack of a record of drug administration or change in concentration of inhalation agent during an episode of hemodynamic abnormality or ischemia. Reasons for non-compliance were failure of the observer to record changes in concentration of inhalation agent, an ischemic or hemodynamic episode too transient to treat or borderline abnormalities diagnosed only on record review. The frequency of treatment noncompliance was not significantly different among the four primary anesthetic agents.

DATA COLLECTION

All data were collected by trained observers who did not participate in patient care. Preoperative data necessary to predict mortality based on the CASS criteria (age, sex, degree of left main coronary obstruction, and indices of global and regional left ventricular function) were recorded.¹⁵ History of chronic hypertension, diabetes, and all chronically administered preoperative drugs with time of last administration were recorded. A copy of the preoperative 12 lead ECG was obtained. (Hewlett Packard® Model 4700 Pagewriter, sensitivity 1 cm/mV, diagnostic quality, 0.05 Hz to 100 Hz). On arrival to the operating

room, traces of ECG leads II and V₅ calibrated to 1 cm/mV and arterial pressures recorded at 25 mm/sec for 15 s were recorded every 2 min until initiation of CPB. Heart rate was calculated from R-R interval. The recording system consisted of Spacelabs® Alpha 14 Model Series 3200 ECG cardule in the monitoring mode (0.5 Hz to 30 Hz) with recorder Model Series 2400 (for 50 mm peak to peak, DC to 30 Hz \pm 1 dB; for 10 mm peak to peak, DC to 100 Hz \pm 3 dB). All instruments complied with American Heart Association recommended standards. Perioperative ischemia was diagnosed by the observer on calibrated paper recordings as horizontal or down sloping ST segment depression of at least 0.1 mV which extended at least 80 msec beyond the J point of the QRS complex. No ST segment elevation in these leads was observed during the prebypass period in any patient. All ECG traces were subsequently reviewed by one investigator (SS) who was unaware of the patient, anesthetic, operative event, or intervention associated with the trace. Times of anesthetic induction, tracheal intubation, skin incision, and sternotomy were noted, as were all drug administrations, including primary anesthetics. The period from arrival to the operating room to induction of anesthesia rarely exceeded 30 min. The period from induction of anesthesia to onset of CPB rarely exceeded 60 min.

SURGICAL PROCEDURE

All operations were performed with a bubble oxygenator, hypothermia to 30° C, and hemodilution. Distal anastomoses of vein grafts and internal mammary artery to coronary arteries were performed first during aortic cross-clamping (ischemia time), at the start of which a single dose of cold (6–10° C) cardioplegic solution was infused into the root of the aorta while the heart was bathed in cold saline. Before removing the aortic cross-clamp, the operating surgeon rated the quality of distal anastomoses and vein grafts according to the following definitions: I—all good anastomotic sites and good quality vein; II—one bad anastomotic site related to presence of plaque or poor quality vein; III—enough poor quality bypasses (artery or vein) to believe the patient would not be improved by operation; and IV—the opinion that operation may be detrimental to the patient. Proximal aortic anastomoses were performed during rewarming after the cross-clamp was removed. Ischemia time, performance of coronary endarterectomy, use of the internal mammary artery, and amount of pharmacologic support required for weaning from CPB were recorded.

POSTOPERATIVE OBSERVATIONS

Hemodynamic patterns, vasoactive drug administration, analgesic drug use, and duration of tracheal intubation were recorded for 24 h after operations. Ten hours

after onset of cardiopulmonary bypass, blood was drawn for quantitative CPK analysis by a modification of the ultraviolet enzymatic determination (Abbott® ABA-100 Method). The MB fraction was determined by ultraviolet examination after isoenzyme separation by electrophoresis (Corning® Electrophoresis Method). While total CPK-MB released after infarction correlates well with infarct size, CPK-MB levels peak 6–16 h after cardiopulmonary bypass and peak levels correlate well with total spillage.^{16–18} A 12-lead electrocardiogram was obtained on the morning of the first postoperative day. Transmural infarction was considered present when new Q waves of at least 0.04 s duration in adjacent leads appeared or when old Q waves extended to new adjacent leads, or when new persistent LBBB appeared *and* when CPK-MB was in excess of 80 U. Diagnosis of PMI required that both criteria were met.

DEATHS

Among the 1,012 patients, 17 (1.7%) died in the hospital. Five were considered to have died as a direct result of PMI occurring within 24 h of operation. These deaths occurred 2–47 days after operation, two from myocardial failure and three from sudden dysrhythmia during recovery from PMI without serious myocardial dysfunction. Three received sufentanil as their primary anesthetic agent, one halothane and one enflurane. Only one had myocardial ischemia during anesthesia and before CPB. All had ECG evidence of new infarction and CPK-MB ranged from 83 to 345 U/L.

The other 12 patients who died had no ECG evidence of PMI and CPK-MB ranged from 0 U/L (7 patients) to 48 U/L. Three patients received sufentanil, four halothane, two enflurane, and three isoflurane. Five died of respiratory failure 3–50 days after operation. Of patients with respiratory failure, three had a history of emphysema, one had chronic congestive heart failure, and one was markedly obese. Two patients died of acute dysrhythmias within 3 days after uneventful operations and recovery. Two died of anemia from hemorrhage after refusing blood transfusions. Three died from multisystem failure 23–120 days postoperatively. In these three patients, the precipitating events were intraoperative neurological complication, small bowel obstruction 1 week postoperatively, and surgical reexploration for hemorrhage with multiple transfusions 1 day postoperatively.

The five patients who died of PMI were included in the group considered to have PMI; the 12 others were included in the group without PMI.

DATA ANALYSIS

All data were analyzed in an AS 9000-IBM Compatible System 3330® computer using the Statistical Analysis System® (SAS). In comparisons of primary anesthetic agents,

differences in continuous variables were tested by analysis of variance or the Kruskal-Wallis test when nonparametric analyses were required. Significance of differences between groups were tested by Student's *t* test. Frequency data were tested by 2×4 Chi-square analysis and between pairs by 2×2 Chi-square analysis corrected for continuity. In addition, stepwise discriminant analysis was used to assess the independent role of patient or operation characteristics in the appearance of myocardial ischemia or PMI. Factors correlating highly with each other were considered first and, when found to be dependently related, were adjusted to avoid destabilization of the analysis by multiple evaluation of the same determinant. For purposes of data treatment, "hypertension" was present when systolic blood pressure was ≥ 180 mmHg, "hypotension" when systolic blood pressure was ≤ 90 mmHg, and "tachycardia" when heart rate was ≥ 110 bpm unless otherwise indicated. This degree of tachycardia had been demonstrated to be the "threshold" level for tachycardia related intraoperative ischemia, the primary issue here.³

Results

RANDOMIZATION

At completion of the study, the primary anesthetic agent was enflurane for 257 patients, halothane for 253, isoflurane for 248, and sufentanil for 254. Adequacy of randomization was examined by comparison of group characteristics that might influence the appearance of ischemia during anesthesia or the incidence of PMI. These characteristics were subgrouped by preoperative disease, chronic drug therapy, hemodynamic values and ischemia on arrival to the operating room and surgical variables (table 1). Of 34 characteristics compared, the only significant differences between primary anesthesia groups were in incidence of history of chronic hypertension and mean preoperative systolic blood pressure. By primary randomization, approximately 25% of each surgeon's patients received each primary anesthetic. There was no significant difference in the frequency with which each of nine anesthesiologists administered each of the primary agents.

OUTCOME

Of 1,012 patients 41 (4.1%) suffered PMI, five of which were fatal (12% of PMI). Hospital mortality from all causes was 1.7% (17 patients), with PMI accounting for 29% of hospital mortality. Data of all patients were pooled and subjected to stepwise discriminant analysis of all factors listed in table 1, in addition to occurrence of intraoperative ischemia and primary anesthetic drug as predictors of PMI. This analysis reaffirmed adverse surgical rating ($F = 9.0$), ischemic clamp time ≥ 40 min ($F = 2.8$), and new perioperative myocardial ischemia ($F = 2.2$) as in-

dependent predictors of PMI. In this population, history of chronic hypertension was also predictive ($F = 3.4$). However, neither primary anesthetic drug nor any other listed factor was independently predictive of PMI. PMI and mortality were not different in the four primary anesthetic groups (table 2).

MYOCARDIAL ISCHEMIA

New myocardial ischemia was present on arrival to the operating room in 297 (29.3%) of all 1,012 patients. When arrival heart rate was less than 90 bpm (880 patients), ischemia was present in 26% compared to 49% when between 90 and 109 bpm in 116 patients ($P < 0.0001$). In 16 patients whose arrival heart rates were ≥ 110 bpm, ischemia was present in nine (56%). Intravenous propranolol was given at arrival to 106 patients and verapamil to ten patients whose heart rates exceeded 89 bpm. Only 4% of 235 patients who received a beta-adrenergic blocking drug with their premedication on the morning of operation had an arrival heart rate > 90 compared with 16% of those who did not ($P < 0.001$).

From induction of anesthesia to onset of CPB, new myocardial ischemia appeared in 310 (30.6%) patients. Ischemia was not significantly more frequent with any primary anesthetic agent (table 3). The relationship of appearance of new ischemia to anesthetic induction and operative stimulation was not different among groups. One-third (33.5%) of all new intraoperative ischemic events was temporally unrelated to any event. In patients with new intraoperative myocardial ischemia, PMI was not significantly more frequent for any one of the four primary anesthetic agents.

INTRAOPERATIVE HEMODYNAMIC PATTERNS

Compared with patients receiving sufentanil, patients who received any of the three volatile agents were more likely to suffer an episode of hypotension and less likely to suffer hypertension (table 4). Differences among volatile agents were not significant. Bradycardia (heart rate < 50 bpm) was rare and not related to any anesthetic technique. As noted previously,³ intraoperative ischemia was not more common in 398 patients with peak heart rates of 90–109 bpm than in 552 with lower peak heart rates (32% versus 28%). Tachycardia (≥ 110 bpm) appeared in 62 patients but was not more frequent with any primary anesthetic. Intraoperative ischemia appeared in 48% of patients with tachycardia compared with 29.5% of those without ($P < 0.005$). Of the hemodynamic abnormalities, only tachycardia was significantly related to new myocardial ischemia compared with patients without any hemodynamic abnormality (table 5). The primary anesthetic did not increase the likelihood of ischemia with any hemodynamic abnormality.

TABLE 1. Group Characteristics after Randomization of 1012 Patients to Four Primary Anesthetic Agents, Expressed as the Mean of All Values or Percent of All Patients with Each Primary Anesthetic

	Enflurane	Halothane	Isoflurane	Sufentanil	P Value*
Number of patients	257	253	248	254	
Preoperative Disease					
Age (years)	58.8	58.4	58.4	59.8	0.27
Age ≥ 60 yr (%)	51.4	47.0	45.6	52.0	0.39
Males (%)	82.9	82.2	85.5	82.3	0.74
LVEDP ≥ 20 mmHg (%)	4.0	2.0	3.6	3.2	0.61
LMCD ≥ 70% (%)	8.2	10.7	7.3	7.9	0.53
Ejection fraction ≤ 30% (%)	9.7	8.3	7.3	7.5	0.74
LV score ≥ 18 (%)	1.2	2.0	2.0	0.8	0.59
Predicted mortality (mean %)	2.98	2.69	2.48	2.36	0.50
History of hypertension (%)	52.1	48.6	39.9	46.9	0.05
History of diabetes mellitus (%)	21.4	26.5	21.0	24.8	0.39
Preoperative heart rate (bpm)	72.6	72.5	73.4	74.4	0.10
Preoperative heart rate ≥ 90 bpm (%)	7.0	6.3	7.7	5.1	0.69
Preoperative systolic BP (mmHg)	125.6	124.6	125.2	128.6	0.04
Preoperative systolic BP ≥ 180 mmHg (%)	0	1.2	0.4	2.0	0.09
Chronic Antianginal Therapy					
Beta adrenergic blocker (%)	53.7	50.6	44.8	44.9	0.11
Administered preoperatively (%)	24.1	25.7	22.6	20.5	0.70
Calcium entry blocker (%)	72.0	78.7	80.6	74.0	0.08
Administered preoperatively (%)	49.0	54.5	47.2	49.6	0.52
Nitrates (%)	59.9	61.7	62.5	57.9	0.72
Administered preoperatively (%)	23.0	28.1	27.4	24.4	0.66
Arrival to Operating Room					
Heart rate (bpm)	71.1	72.2	72.6	71.6	0.52
Heart rate ≥ 90 bpm (%)	14.0	15.0	10.9	11.4	0.32
Heart rate ≥ 110 bpm (%)	1.6	0.8	2.8	1.2	0.40
Systolic BP (mmHg)	150.7	152.7	148.1	152.6	0.22
Systolic BP ≥ 180 mmHg (%)	13.6	19.0	12.9	18.1	0.27
Systolic BP ≤ 90 mmHg (%)	0.4	1.6	1.6	1.2	0.56
New ST segment depression (%)	25.3	32.4	31.8	28.0	0.24
Coronary Operation					
Number CABG performed (mean)	3.54	3.51	3.49	3.50	0.95
CABG ≥ 4 (%)	54.1	49.8	50.4	47.7	0.53
IMA graft (%)	76.3	81.8	82.7	82.7	0.19
Coronary endarterectomy (%)	9.7	10.3	9.7	10.6	0.98
Ischemic clamp time (min)	34.5	35.1	34.8	36.3	0.50
Ischemic clamp time ≥ 40 min (%)	30.0	27.7	30.7	33.1	0.62
Surgical rating ≥ 2 (%)	17.9	15.8	15.8	20.5	0.45

LVEDP = left ventricular end-diastolic pressure; LMCD = left main coronary disease percent occlusion; LV Score = left ventricular score;¹⁵ CABG = number of coronary artery bypass grafts; IMA = internal

mammary artery.

* For continuous data, by analysis of variance or Kruskal-Wallis test; for frequency data by Chi-square contingency table analysis.

To determine predictors of intraoperative myocardial ischemia, stepwise discriminant analysis was carried out utilizing all data of table 1, all intraoperative hemodynamic data, and primary anesthetic drug. Significant independent predictors of intraoperative myocardial ischemia included failure to receive preoperative beta adrenergic blocking drugs (F = 3.3), tachycardia upon arrival to the O.R. (F = 4.0), number of CABG performed (F = 7.6), chronic use of nitrates (F = 7.7), good left ventricular function (F = 8.6), intraoperative tachycardia (F = 9.2), and new ischemia on arrival to the operating room (F = 49.7). Of 278 patients with ischemia on arrival, ischemia reappeared or worsened during anesthesia in 46.0% compared with an incidence of ischemia of 24.2% in pa-

tients with no arrival ischemia (P < 0.0001). Neither primary anesthetic drug nor anesthesiologist was a predictor of intraoperative myocardial ischemia.

OTHER OBSERVATIONS

The role of primary anesthetic on other aspects of anesthetic management was examined only in patients who suffered neither PMI or death (table 6). Ease of weaning from CPB was not affected by primary anesthetic. In the first 24 postoperative hours, patients who received sufentanil tended to have less hypertension and needed less vasodilator therapy and less analgesic drugs, but required a longer period of tracheal intubation. The three volatile

TABLE 2. Incidence of Postoperative Myocardial Infarction (PMI) and In-hospital Mortality in Four Groups of CABG Patients Different Only in Primary Anesthetic Agent

	Enflurane	Halothane	Isoflurane	Sufentanil	P Value
Patients	257	253	248	254	
PMI	12 (4.7%)	9 (3.6%)	10 (4.0%)	10 (3.9%)	0.94
Deaths	3 (1.2%)	5 (2.0%)	3 (1.2%)	6 (2.4%)	0.66

agents did not differ among themselves. As in our previous studies, postoperative CPK-MB spillage correlated strongly with ischemic clamp time (CPK-MB = 3.74 + 0.22 ischemia time, $r = 0.6556$, $P < 0.0001$). Primary anesthetic drug did not influence the degree of CPK-MB spillage (table 6).

POWER ANALYSIS

In patients grouped by the four primary anesthetic agents, the range of incidence of intraoperative ischemia was 28.0–33.5%, of PMI 3.6–4.7%, and of mortality 1.2–2.4%. Assuming an 80% probability of finding these low-high values significantly different between primary anesthetic agents, the total number of patients required would be 1,715 for ischemia, 7,844 for PMI, and 3,287 for mortality. Conversely in the 1,012 patients actually studied a 14% difference in the incidence of intraoperative myocardial ischemia would have been significant with 80% probability.

Discussion

For more than a decade, a lively debate has centered around the relative merits of potent narcotics compared with potent inhalation agents, such as halothane and, particularly, isoflurane, as primary anesthetics for patients undergoing CABG. Advocates of narcotics point out the lack of myocardial depression and the circulatory stability

TABLE 3. Incidence of New Intraoperative Myocardial Ischemia in Four Primary Anesthetic Groups and Temporal Relationship to Operative Events. Differences among Groups Were Not Significant for Any Row.

	Intraoperative Ischemia				P Values
	Enflurane (%)	Halothane (%)	Isoflurane (%)	Sufentanil (%)	
New Myocardial Ischemia	28.0	32.8	33.5	28.4	0.40
Ischemia associated with*					
Anesthetic induction	18	19	16	25	0.25
Operative stimulation†	47	48	47	46	0.95
No specific event	35	33	37	29	0.95

* Percent of patients with ischemia.

† Tracheal intubation, skin incision, or sternotomy

TABLE 4. Hemodynamic Stability from Induction of Anesthesia to Onset of Cardiopulmonary Bypass in 1,012 Patients who Received Four Different Primary Anesthetics

	Primary Anesthetic				P Value
	Enflurane*	Halothane*	Isoflurane*	Sufentanil*	
Patients	257	253	248	254	
Percent of patients with hemodynamic abnormality					
Tachycardia (≥ 110)	4.3	6.3	4.8	9.1	0.110
Hypertension	17.1	15.8	15.3	33.5	0.001
Hypotension	56.0	61.3	58.5	29.5	0.001
None of Above	32.3	26.1	29.8	42.9	0.001

* Totals of columns exceed 100% because some patients had more than one abnormality at the same or different times.

during anesthesia. Advocates of the inhalation agents point out the benefits of myocardial depression in most patients undergoing CABG and the inability of narcotics to block the hypertensive responses to surgical stimulation. Both sides support their position with data that apply to the process of anesthesia, particularly the hemodynamic responses associated with the anesthetic and with surgical stimulation during anesthesia. In the absence of outcome data, a healthy future for the debate was assured. The purpose of this study was to provide some missing outcome data by a carefully designed prospective study.

During planning of this investigation, we were aware of published studies that suggested that both halothane and isoflurane might have deleterious effects on myocardium supplied by a partially occluded coronary artery. Lowenstein *et al.*¹⁹ administered increasing doses of halothane to dogs with critical coronary stenosis and produced regional ischemic ventricular dysfunction, possibly the result of inadequate perfusion pressure during uncomplicated halothane anesthesia. During administration of 1% isoflurane to patients with coronary artery disease, Reiz *et al.*²⁰ noted regional myocardial ischemia, presumably by a combination of reduced coronary perfusion pressure and redistribution of coronary blood flow away from areas supplied by constricted arteries. In both studies, agent-specific effects on the coronary circulation that might adversely affect coronary flow in patients with diseased vessels were suggested. The current study was therefore designed to compare three inhalation agents with each other and a narcotic-based anesthetic rather than one volatile drug with one narcotic. This was fortunate in view of subsequent animal and human data suggesting isoflurane uniquely predisposes to coronary steal^{21–25} and an editorial recommendation that isoflurane not be used in patients with coronary artery disease.²⁶ A portion of these outcome data are responsive to this recommendation.

The study was further designed to mimic clinical practice rather than to study each drug administered as the sole anesthetic, which is never done in practice except for high-dose narcotics. In all patients, therefore, anesthesia was induced with intravenous drugs to provide a smooth induction and to permit immediate introduction of the volatile anesthetic to patients selected to receive it. Dose of the inhalational agent was governed entirely by hemodynamic response and was administered almost continuously in some concentration until onset of CPB. The narcotic, on the other hand, was administered as the sole agent in the fashion of its typical use. The large dose of sufentanil, $28.2 \pm 4.3 \mu\text{g}/\text{kg}$, was selected to avoid a retrospective issue of inadequate dosage. Management of all other aspects of anesthetic care of all patients was by a standardized protocol applied to all patients.

The technique of randomization incorporated in the study was highly successful. By design, primary anesthetics were randomized for each surgeon, and anesthesiologists used each anesthetic equally. The four groups compared for primary anesthetic agent were remarkably homogeneous for preoperative characteristics, severity of cardiac disease, chronic drug therapy, characteristics on arrival to the operating room, and surgical factors that might independently contribute to hemodynamic changes, new myocardial ischemia, or adverse outcome (table 1). Compared with CABG populations of our previous studies, patients in this study were older and had more advanced disease (58.9 yr and 2.63% predicted mortality versus 56.1 yr and 2.35% predicted mortality for 1962 previously reported patients¹⁻³). Despite this difference, the frequency of new ischemia on arrival to the operating room, intraoperative ischemia, PMI, and mortality are almost identical to those reported earlier.

The study was planned to include 1,000 patients and did not seek a significant difference in PMI rates between groups. This study was predicated on our previous dem-

TABLE 5. Incidence of Intraoperative Myocardial Ischemia Among Patients who Experienced a Single or No Intraoperative Hemodynamic Abnormality.* Difference Among Groups Were Not Significant for Any Row When Compared as Four Groups or as Pooled Volatile Agents Compared to Sufentanil

	Enflurane (%)	Halothane (%)	Isoflurane (%)	Sufentanil (%)	All Patients (%)
Incidence of ischemia in patients with Tachycardia (n = 62)	46	62	50	39	48.4†
Hypertension (n = 123)	38	33	48	31	35.8
Hypotension (n = 428)	26	28	32	31	27.3
None of above (n = 332)	25	30	30	27	27.7

* All patients with heart rate ≥ 110 were included in tachycardia group without consideration of any change in blood pressure. Patients with separate episodes of both hypo- and hypertension were excluded (n = 67).

† $P < 0.005$ when compared to patients with no abnormality.

onstration that perioperative myocardial ischemia, whether on arrival or during anesthesia, was a significant predictor of PMI. By using myocardial ischemia, a high-frequency event (35–55% of patients) to predict a low-frequency outcome (4% of patients), we believed an appreciable reduction in myocardial ischemia, and, by inference, PMI, would be a significant contribution to clinical care. In this study of 1,000 patients, a 15% difference in myocardial ischemia would have been statistically significant with a power of 0.8, and inferred at least a 1% decrease in PMI. We did not believe the continuation of this study to validate statistically a 5% reduction about a mean of 30% incidence of intraoperative ischemia would represent an important contribution to clinical care, especially because at least two other highly significant predictors of PMI also operate.

TABLE 6. Observations following CPB and during Postoperative Care of 959 Patients who Did Not Suffer PMI or Death

	Primary Anesthetic Agent				P Value
	Enflurane	Halothane	Isoflurane	Sufentanil	
Uncomplicated weaning from CPB* (%)	66.3	68.7	69.8	64.7	0.629
Systolic BP ≥ 200 mmHg in PAR (%)	25.9	21.2	22.1	15.8	0.055
Vasodilator therapy in PAR (%)	21.4	21.7	21.3	11.7	0.011
Analgesic administration in PAR (%)	84.7	79.5	84.3	48.6	0.001
Duration of tracheal intubation (hours)†	14.5 ± 6.3	16.8 ± 7.2	14.7 ± 5.4	22.8 ± 12.3	0.001
Mean CPK-MB (IU)†	12.8 ± 23	14.7 ± 29	13.8 ± 25	13.7 ± 26	0.700

* No pharmacologic or mechanical support required for termination of CPB.

† Mean \pm SD.

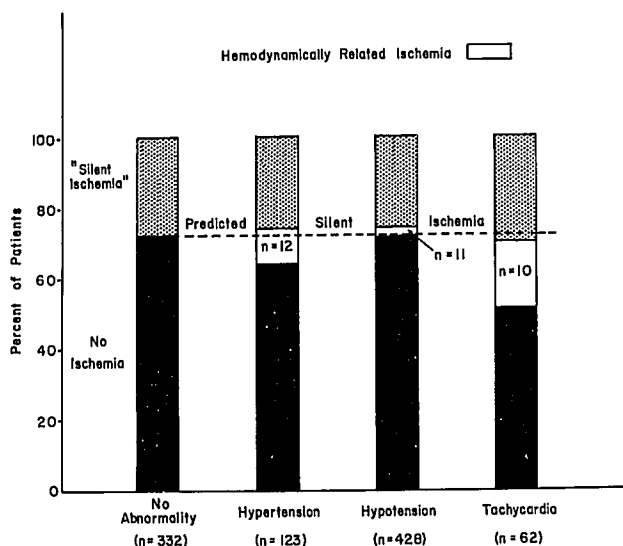


FIG. 1. Relationship of 283 episodes of new myocardial ischemia appearing during anesthesia to hemodynamic abnormalities in 945 patients undergoing CABG. Sixty-seven patients with separate episodes of both hypo- and hypertension were excluded (table 5). Ischemia in patients without hemodynamic abnormality and ischemia not temporally related to the specific hemodynamic abnormality are assumed to represent "silent ischemia." The expected incidence of "silent ischemia" in all groups is 27.7% based on patients with no hemodynamic abnormality and is represented by the horizontal line of identity. Only 33 (11.7%) ischemic episodes were related to a hemodynamic abnormality occurring within the 5 min before or at the time of ischemia. Only these temporally related episodes are postulated to be the consequence of anesthesia management, and all other ischemia to be a characteristic of the coronary disease process present in about one-third of patients presenting for CABG.

Based on myocardial ischemia and PMI, this study fails to provide any basis for selecting or rejecting any of these primary anesthetic agents for use in elective CABG in patients. The hemodynamic consequences of each primary anesthetic agent were as previously described and expected. Hypotension was twice as likely in patients receiving volatile anesthetics, and hypertension was twice as likely in those receiving sufentanil. Neither less frequent hypotension nor less frequent hypertension was rewarded by a lower frequency of new myocardial ischemia. As previously noted, tachycardia increased the likelihood of myocardial ischemia, and no primary anesthetic either attenuated this relationship or was associated with less tachycardia. In patients who received isoflurane, myocardial ischemia was not more common with or without hypotension. The group of 248 patients who received isoflurane included 164 whose systolic blood pressure was less than 90 mmHg at some time during its administration. Yet, new myocardial ischemia, PMI, and mortality were not more frequent in these patients, nor in patients who received halothane with or without its characteristic hypotension.

The results of this study are entirely consistent with, and provide further support for, the hypothesis we previously proposed.^{2,3} In our population, postoperative myocardial infarction after CABG was consistently related to one perioperative patient predictor (appearance of new myocardial ischemia) and two surgical predictors (technical quality of coronary anastomoses and prolonged ischemia time, both of which may be related to the experience of the surgeon). We postulated that, because most new ischemia we observed was not related to any hemodynamic change, it was the same phenomenon as the ischemic episodes without pain or hemodynamic change suffered by patients with coronary artery disease during their usual daily activities.²⁷ These episodes, labeled silent myocardial ischemia, were identical to painful myocardial ischemia in their association with decreased coronary perfusion, wall motion abnormalities, and response to antianginal treatment.²⁸ To date, three studies of patients with unstable angina have clearly described a poorer short-term prognosis for infarction or need for revascularization in patients with high frequency of silent ischemia compared with those with rare silent ischemia.²⁹⁻³¹ In our patients selected for CABG because of failure of medical therapy, silent ischemia was common, being present in 29.3% of all patients on arrival to the operating room (table 1). We now further postulate that patients with a high frequency of silent ischemia have a poorer prognosis for infarction with or without operation, just as in unstable angina, and that this disease characteristic accounts for the powerful predictive value of new myocardial ischemia for PMI.

After induction of anesthesia, the background of silent ischemia continues. In our patients, 332 experienced no hemodynamic abnormality from induction of anesthesia to start of CPB, yet new ischemia appeared in 27.7% (table 5, fig. 1). We believe this background silent ischemia occurs with equal frequency in patients who also have hemodynamic instability during their anesthesia. We found no temporal relationship between the hemodynamic abnormality and the appearance of the ischemic episode in 26.0% of patients with hypertension at some time during anesthesia, in 25.2% of patients with hypotension, and in 32% of patients with tachycardia (fig. 1). A temporal relationship between ischemia and hemodynamic abnormality occurred in only 33 patients, and only in patients with tachycardia (≥ 110 bpm) was the relationship strong enough to demonstrate a significantly greater incidence of ischemia compared to hemodynamically stable patients (table 5). Based on these assumptions, 33 patients at most, and more likely only the 10 patients with tachycardia (1% of the 1,012 studied), were recruited from the lesser risk group of no intraoperative ischemia to the higher risk group with ischemia by virtue of anesthetic management. As originally postulated, perioperative ischemia was pri-

marily a characteristic of the underlying coronary artery disease rather than the consequence of anesthetic management. Although most patients with new myocardial ischemia are at increased risk by virtue of their disease, additional patients at otherwise lesser risk can be recruited to higher risk when tachycardia is not prevented before or during anesthesia. In the clinical situation studied here, the major role of the anesthesiologist in preventing PMI remains limited to control of heart rate, primarily by beta-adrenergic blocking agents.

The present study was not designed to examine the role of intraoperative treatment of silent ischemia by antianginal drugs or by hemodynamic manipulation on the incidence of PMI. Those who advocate more sensitive devices for detection or more elaborate treatment options need to document their value in the outcome of CABG against a background that accounts not only for silent ischemia, but also for the important surgical predictors in their population, which may not be the same as in our population.

We conclude that, despite important differences in intraoperative hemodynamic conditions and postoperative care of patients receiving different primary anesthetic agents for CABG, none of the four drugs considered here had a positive or negative, primary or secondary effect on occurrence of new myocardial ischemia, frequency of intraoperative tachycardia, relationship of ischemia to any specific hemodynamic abnormality, ease of weaning from bypass, nonspecific myocardial necrosis secondary to aortic cross-clamping, rates of PMI, or mortality. In this study, the differences in process variables of anesthesia, blood pressure responses, and duration of postoperative intubation were as expected from the known pharmacologic effects of the primary anesthetic agents.

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ADDENDUM

Since preparation of this manuscript, an editorial by Lowenstein and McPeck³² commented on the results of our third study of CABG patients⁹ published simultaneously with the results of the first study of similar patients by the SPI Research Group.³³ The editorial focused on differences in the incidence of ischemia noted in the two studies and especially the difference in incidence during the period between arrival to the operating room and induction of anesthesia. We reported an incidence of 27% of 444 patients,⁹ Knight *et al.*³³ reported 4% of 50 patients. Possible reasons for the difference were thoroughly discussed in the editorial and in Discussion of the Knight *et al.* paper. We have nothing to add to clarify the question except the obvious difference in methods used to detect ischemia. In our studies, ischemia was considered present when ST segment was displaced compared to its position on the standard preoperative 12-lead

ECG recorded from each patient sometime after hospital admission. Knight *et al.* used a Holter monitor with computer analyzed tapes. At issue may be the greater sensitivity of our traditional method of diagnosing myocardial ischemia compared with an automated one. Kotter *et al.*,³⁴ using an ST segment trend monitor applied when the patient arrived in the operating room, also found a low incidence of ischemia. Only one of their 247 patients had ischemia before induction of anesthesia and only 8% had ischemia during the period between anesthesia induction and onset of CPB (contrasted with 14% for Knight *et al.* and 34% for Slogoff and Keats). In groups of CABG patients ranging in size from 20 to 81 patients,^{9,20,55,56} the incidence of intraoperative ischemia ranged from 26% to 69% using a visual method similar to ours. In only one study was a Holter monitor used to diagnose intraoperative myocardial ischemia in 50% of 20 patients undergoing CABG.³⁷ In this study, the Holter tapes were visually rather than computer scanned. We believe a comparison of methods for sensitivity will define the issue.

Despite the difference in absolute incidence of ischemia, the data of Knight *et al.* nicely confirm other important aspects of our data and predictions. In our four studies to date, we observed ischemia on arrival and before anesthesia in 18.8%, 26.5%, 27.5%, and 29.3% of patients, or 24.6% of 2974 patients about to undergo CABG. We postulated in our initial report that this high incidence represented the same phenomenon as silent myocardial ischemia known to be associated with coronary artery disease in nonsurgical patients. Through Holter monitoring of patients before CABG, this high incidence has been confirmed as 42% of 50 patients by Knight *et al.*,³³ 18% of 33 patients by Yousef *et al.*,³⁸ and 33% of 18 patients by Wilton *et al.*,³⁹ or 32.7% of 101 patients. Based on presentations at recent meetings, a similar incidence appears in patients scheduled for vascular operations. Knight *et al.* also confirmed the absence of a strong relationship between hemodynamic abnormality and the occurrence of ischemia and added a new observation, the high incidence of ischemia in the postoperative period. Their high incidence of both postoperative ischemia and myocardial infarction may be interpreted as supporting the role of surgical factors rather than perioperative myocardial ischemia as primary predictors of postoperative myocardial infarction.

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