Anesthesiology
74:838–847, 1991

Isoflurane Anesthesia and Myocardial Ischemia: Comparative Risk versus *Sufentanil Anesthesia in Patients Undergoing Coronary Artery Bypass Graft Surgery*

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Whether isoflurane has the potential to produce coronary artery steal and associated myocardial ischemia is still controversial. Previous studies addressing this issue in humans did not purposefully control hemodynamics or use continuous measures of myocardial ischemia. The authors used transesophageal echocardiography (TEE) and continuous Holter electrocardiography (ECG) to study the relative risk of myocardial ischemia during isoflurane or sufentanil anesthesia under strict control of hemodynamics in 186 high-risk patients undergoing elective coronary artery bypass graft (CABG) surgery. Overall, hemodynamics were well controlled (increased heart rate = 9.8%; increased systolic blood pressure = 7.1%; decreased systolic blood pressure = 10.8% of total prebypass time compared with preoperative baseline values), with no difference between the two anesthetics. In the 162 patients with interpretable TEE recordings, moderate to severe TEE ischemic episodes (grade change ≥ 2) developed in 33 (21%) during the prebypass period, with no difference between isoflurane (12 of 56 = 21%) and sufentanil (21 of 106 = 20%) (P = 0.97). The duration and severity of TEE episodes were not significantly different between the two groups. No correlation was observed between TEE ischemic episodes and isoflurane concentrations (range, 0.47–1.75%). In the 181 patients with interpretable ECG recordings, ECG evidence of ischemia developed in 34 (19%) during the prebypass period, with no difference between isoflurane (12 of 59 = 20%) and sufentanil (22 of 122 = 18%) (P = 0.87). The duration and severity of electrocardiographic ischemic episodes were also similar in patients receiving either isoflurane or sufentanil. Four of the 62 patients (6%) who received isoflurane had an adverse cardiac outcome *versus* 15 of 124 patients (12%) who received sufentanil (P = 0.34). The authors' findings demonstrate that, when hemodynamics are controlled, the incidence of myocardial ischemia (TEE or ECG) during isoflurane and sufentanil anesthesia is similar. (Key words: Anesthesia: cardiac. Anesthetics, intravenous: sufentanil. Anesthetics, volatile: isoflurane. Heart: coronary artery disease; myocardial ischemia. Monitoring: blood pressure; hemodynamics; Holter electrocardiography; pulse rate; transesophageal echocardiography. Surgery: coronary artery bypass graft.)

WHETHER ISOFLURANE has the potential to produce coronary artery steal and associated myocardial ischemia is still controversial.[1,2] Although some studies suggest the safety of isoflurane in at-risk patients undergoing surgery,[3–5] others have shown that isoflurane is a coronary vasodilator in both animals and humans.[1,6–9] and that isoflurane can cause redistribution of myocardial blood flow (intercoronary and transmural steal) in specific animal models.[7,8] Ischemic changes (regional mechanical dysfunction and redistribution of myocardial blood flow) have been demonstrated in canine preparations,[8,10] and association between isoflurane and markers of myocardial ischemia (electrocardiographic and metabolic changes) has been observed in at-risk patients undergoing surgery.[1,11–13] Because more than 400,000 cardiac surgical procedures are performed annually in the United States and 3 million of 25 million noncardiac surgical procedures are performed in patients who have or are at risk for coronary artery disease,[14] it is important that we know whether isoflurane indeed produces myocardial ischemia because, if it does, its use should be limited in such high-risk populations.

Previous studies have helped us to understand isoflurane's ischemic potential but have several limitations, including the number of patients studied,[1,4,5,11–13] the lack of hemodynamic control during the study period,[1,11–13] the lack of comparison of isoflurane to another anesthetic,[1,4,5,11,12] and the use of intermittent- or single-modality measures of ischemia.[1,4,5,11–13] In contrast, we designed a study using continuous and sensitive measures of ischemia (transesophageal echocardiography [TEE] and Holter electrocardiography [ECG]) to assess the relative risk of myocardial ischemia during isoflurane *versus* sufentanil anesthesia, under conditions of strict hemodynamic control.

Materials and Methods

After institutional approval and informed consent were obtained, 186 patients (185 men and 1 woman, 37–79 yr of age) scheduled for elective coronary artery bypass graft

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Received from the Departments of Anesthesia and Medicine of the University of California, San Francisco, and the Veterans Affairs Medical Center, San Francisco, California. Accepted for publication January 7, 1991. Supported in part by grants from the National Institutes of Health (RO1-HL36744) and the Alberta Heritage Foundation for Medical Research. Presented in part in abstract form at the Annual Meeting of the American Society of Anesthesiologists, 1989 (New Orleans, Louisiana).

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(CABG) surgery at the San Francisco Veterans Administration Medical Center between August 1987 and March 1990 were randomized to receive isoflurane or sufentanil anesthesia. The demographic and clinical data collected for each patient included a history of prior myocardial infarction, previous CABG surgery or angioplasty, hypertension, diabetes mellitus, unstable angina, and preoperative cardiac medications. Preoperative ejection fraction was determined by ventriculography and the number of significant coronary arterial stenoses noted. Significant stenosis was defined as a 70% or greater luminal stenosis of the left anterior descending, left circumflex, or right coronary artery and a 50% or greater diameter stenosis of the left main coronary artery.

Anesthetic Management

The baseline measurements of heart rate (HR) and systolic blood pressure (SBP) were determined by averaging the last five preoperative values obtained for each variable. Measurements of HR and SBP were obtained during the 48-h preoperative period while the patients were on maximal medical therapy. Routine clinical monitors included seven-lead ECG and radial-artery and pulmonary-artery catheters. The end-tidal isoflurane concentration was continuously monitored by mass spectrometry and stored in a microcomputer. All clinicians providing direct patient care were blinded to the research information obtained from the echocardiographic and specialized ECG monitoring.

Patients received diazepam (0.1 mg/kg) and morphine sulfate (0.1 mg/kg) as preanesthetic medication, and all cardiac medications were continued until the time of operation. Sixty-two patients received isoflurane (mean end-tidal isoflurane concentration range, 0.88% ± 0.31%) and 124 patients received sufentanil (5–10 $\mu g/kg$ followed by an infusion rate of 0.07 $\mu g \cdot kg^{-1} \cdot min^{-1}$) as the primary anesthetic during the prebypass period. Patients given sufentanil were allowed to receive a maximum of 0.5 mg/kg of diazepam and those receiving isoflurane, a maximum of 0.5 mg/kg of diazepam, 7 mg/kg of sodium thiopental, and 7.5 $\mu g/kg$ of fentanyl as adjuvant anesthetics during anesthetic induction. Tracheal intubation was facilitated with the use of muscle relaxants. All patients received 100% inspired oxygen to maintain Pa_{O_2} levels greater than 70 mmHg, and ventilation was controlled to maintain Pa_{CO_2} levels between 35 and 45 mmHg. The lungs of all patients were ventilated with a tidal volume of 10–15 ml/kg.

The anesthesiologists were requested to maintain HR within 20% and SBP within ±20% of preoperative baseline values throughout the prebypass period. If the anesthesiologist judged anesthetic depth to be inadequate, inspired isoflurane concentrations were increased; and, in those who received sufentanil, an intravenous bolus of 1 $\mu g/kg$ sufentanil was supplemented, followed by an increased infusion rate of 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$. This maneuver was repeated for three cycles, as needed, throughout the prebypass period. After these maneuvers, any hemodynamic aberrations occurring in either group were treated with vasodilators and beta-adrenergic blocking agents, as needed. The administration of vasodilators, vasopressors, beta-adrenergic blocking agents, and inotropic drugs was recorded.

During the postbypass period, patients who received isoflurane before bypass were given morphine sulfate (mean, 42 ± 38 mg; range, 0–145 mg) and those given sufentanil were further randomized to receive sufentanil infusion (62 patients at 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$) or morphine sulfate (62 patients: mean, 38 ± 42 mg; range, 0–150 mg). Only data from the prebypass period are presented, to allow comparison between sufentanil and isoflurane anesthetics.

Transesophageal Echocardiography

Immediately after tracheal intubation, a gastroscope tipped with either a 3.5-MHz (Diasonics Inc., Milpitas, CA) or a 5-MHz phased-array transducer (General Electric Co., Milwaukee, WI) was introduced into the esophagus. The transducer was positioned and maintained at the level of the midpapillary muscles to obtain a short-axis view of the left ventricle. Echocardiographic (TEE) data were recorded continuously onto videotapes during the prebypass period (*i.e.*, from completion of tracheal intubation to the onset of cardiopulmonary bypass).

The real-time videotape was edited to obtain samples for analysis. Echocardiographic samples of 60 s duration were obtained every 15 min throughout the prebypass period. Additionally, samples were obtained at other prespecified times to determine whether anesthetic or surgically imposed stresses had any immediate effect on regional wall motion. During the prebypass period, samples were obtained immediately after tracheal intubation and at 4 min before and 1 and 6 min after each of the following surgical events: skin incision, sternotomy, pericardiotomy, and aortic and right atrial cannulation.

The short-axis, cross-sectional image was divided into four segments, with the use of the papillary muscles as guides. This floating-reference system compensated for translational and rotational movements of the heart. A segment was considered suitable for wall-motion analysis if 70% of its entire endocardial outline was visible continuously throughout systole and diastole. All samples were visually analyzed by two investigators by consensus; these investigators were blinded to patient identity, clinical outcome, and time of sampling. The wall motion of each of the four segments was graded as follows: 0 = normal, 1

= mild hypokinesis, 2 = severe hypokinesis with myocardial thickening, 3 = akinesis, and 4 = dyskinesis. Myocardial thickening was estimated by visual inspection in real time and slow motion. Each patient's best prebypass wall motion score was used as his or her baseline score. A "TEE episode"‡‡ suggestive of ischemia was defined by regional wall motion worsening two or more grades and lasting 1 min or longer. The interobserver variability for definition of a TEE ischemic episode was 3% and intraobserver variability was 2% (for both observers), as previously reported.[15]

Electrocardiography

Electrocardiographic monitoring was performed with a two-channel AM Holter® ECG recorder (Marquette Electronics, series 8500) for two days preoperatively (baseline) and also from the time of anesthetic induction to the onset of cardiopulmonary bypass. The frequency response met the American Heart Association specification for ST changes, the cutoff limit being 0.05 Hz for low frequency and 80 Hz for high frequency. Two bipolar leads, CC5 and modified CM5, were used. Each complete ECG recording on Holter tape was scanned visually with the use of an ECG analysis system (Marquette series 8000). All abnormal QRS complexes (*e.g.*, ventricular ectopic beats and conduction abnormalities) were excluded. A continuous two-lead ST-segment trend was then generated for the entire tape. The baseline ST-segment level was defined as the average ST-segment during a stable period (usually 1 h) preceding each episode. All possible ischemic episodes were reviewed and verified by two investigators who were blinded to patient's identity and outcome. An electrocardiographic ischemic episode was defined as reversible ST-depression $\geq$ 0.1 mV from baseline at J + 60 ms, or >0.2 mV ST elevation at the J-point lasting for at least 1 min. During tachycardia, when J + 60 ms decreased within the T wave, the time after the J-point was shortened to a minimum of J + 40 ms. The characteristics of each electrocardiographic ischemic episode, including the magnitude (ST-segment), duration (episode duration), area-under-the-ST-segment-time-curve (AUC), as well as the ischemic burden (minutes of ischemia/hours monitored), were also determined.

Hemodynamics

Intraoperatively, SBP and diastolic blood pressure (DBP) were monitored continuously with the use of radial-artery catheters in all 186 patients. HRs were derived from the ECG tracings. Pulmonary artery systolic and diastolic pressures were monitored continuously in 183 patients (three patients did not have interpretable tracings). SBP, DBP, mean arterial pressure, pulmonary artery pressure, and HR were measured continuously on patient entry into the operating room and stored in a microcomputer (Toshiba T1000; Toshiba Corporation, Tokyo, Japan) using a digital interface system. All hemodynamic data also were recorded continuously onto hard copy at 1 mm/s with a four-channel strip chart recorder (4-Inch Direct Digital Writer®; Marquette) linked to the hemodynamic monitor (Marquette 7010; frequency response, 0.05–120 Hz). Hemodynamic data were averaged every 60 s and entered into the microcomputer. The zero reference point was located 5 cm posterior to the sternal angle in a direction perpendicular to the frontal plane of the chest. The time clocks on the TEE, Holter monitor, and hemodynamic recorder were synchronized before anesthetic induction.

The hemodynamic data were analyzed as follows: 1) HR, SBP, DBP, and pulmonary artery diastolic pressure (PAD) were sampled from the computer every 60 s; 2) data on the hard copy were reviewed to assure that artifacts (such as erroneous values resulting from blood drawing or flushing of catheters) were excluded from analysis; and 3) the data were entered into a computer spreadsheet (Statview 512+®; Brainpower, Calabassas, CA), and the frequency distributions for HR and SBP were determined for the entire prebypass period for each patient.

We defined significant hemodynamic changes as >20% increases in HR, SBP, or PAD; or >20% decreases in SBP or DBP.

Operative Technique

Cardiopulmonary bypass was performed with the use of a bubble oxygenator, hemodilution, and moderate systemic hypothermia (26–28° C). Multidose cold blood (8° C; hematocrit 20–25%) with potassium cardioplegia (20 mEq/l) and topical saline/ice slush was used for myocardial protection during cardiopulmonary bypass. Distal anastomoses were performed during continuous aortic cross-clamping, followed by proximal vein grafting during partial aortic occlusion. One hundred seventy-seven patients received vein grafts, and 177 patients received internal mammary-artery grafts to either the left anterior descending or the first diagonal coronary artery. The pericardium was left open in all patients.

The quality of the bypass grafts was assessed by surgeons who were unaware of the echocardiographic and hemodynamic findings. The grafts were graded qualitatively as poor, fair, very good, and excellent.

‡‡ The term "ischemia" is used to indicate those TEE or ECG changes suggestive of ischemia, with consideration that without an independent measure of myocardial blood flow relative to demand, not all such changes are necessarily indicative of ischemia.

Outcome Measurements

Both 12-lead ECG and creatinine phosphokinase (CPK)-MB isoenzyme concentrations were obtained preoperatively (control) and daily for the first three postoperative days. Adverse major outcomes were myocardial infarction, ventricular failure, or cardiac death. These were defined as follows: 1) myocardial infarction: new Q waves (≥ 40 ms, 25% R-wave) on 12-lead ECG *and* CPK-MB isoenzyme concentration ≥ 50 U/l; 2) ventricular failure: cardiac index < 2 $l \cdot min^{-1} \cdot m^{-2}$ requiring an intraaortic balloon pump; and 3) cardiac death: death attributed to cardiac cause during the period of hospitalization. A cardiac cause was defined as dysrhythmia or congestive heart failure resulting from a cardiac condition.

Statistical Methods

Chi-squared analysis with continuity correction was applied to categoric data. Student's *t* test was used to test the difference between the means in the two groups. Nonparametric data were assessed by the Mann-Whitney U Test. Differences in HR and blood pressure were assessed by one-way analysis of variance using repeated measures. $P < 0.05$ (two-sided) identified significant differences.

Results

Overall, interpretable intraoperative TEE data were obtained for 162 of the 186 patients studied. Interpretable preoperative Holter data were obtained for 176 patients, and interpretable intraoperative Holter data were obtained for 181 patients. Although the two groups were unequal in size, the demographic data and preoperative medications were similar in patients receiving either anesthetic (table 1).

TABLE 1. Clinical Data in 186 Patients

	Isoflurane (n = 62)	Sufentanil (n = 124)
Age (yr)	61 ± 9 (40–79)	62 ± 8 (37–79)
Prior myocardial infarction	38 (61%)	78 (63%)
Prior CABG	2 (3%)	10 (8%)
Prior angioplasty	6 (11%)	13 (10%)
Hypertension	42 (68%)	68 (55%)
Diabetes mellitus	13 (23%)	35 (28%)
Unstable angina	41 (66%)	68 (55%)
Preoperative EF by angiography	54% ± 14%	53% ± 15%
Medications:		
Nitrates	58 (94%)	114 (92%)
Calcium channel blockers	52 (84%)	104 (84%)
β-adrenergic blockers	36 (58%)	63 (51%)
Number of stenosed vessels		
One	3 (5%)	11 (9%)
Two	15 (24%)	33 (27%)
Three or more	44 (71%)	80 (65%)
Left main	14 (23%)	43 (35%)

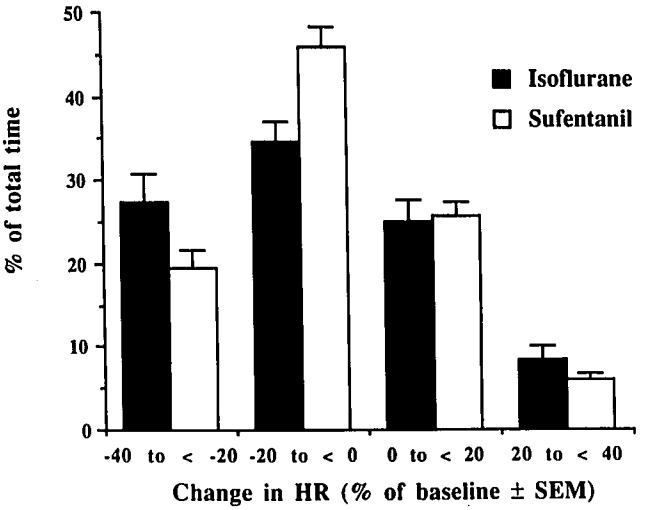

FIG. 1. The frequency distributions of heart rate (HR) as percentage changes from preoperative baseline values in 186 patients.

Hemodynamic Control

Hemodynamics were well controlled during the prebypass period (increases in HR = 9.8%, increases in SBP = 7.1%, and decreases in SBP = 10.8% of total monitoring time during the prebypass period compared with preoperative baseline values) (figs. 1 and 2), with no difference between the two anesthetic groups.

TEE Episodes

Moderate to severe TEE ischemic episodes (grade change ≥ 2) occurred in 33 of 162 patients (21%), with

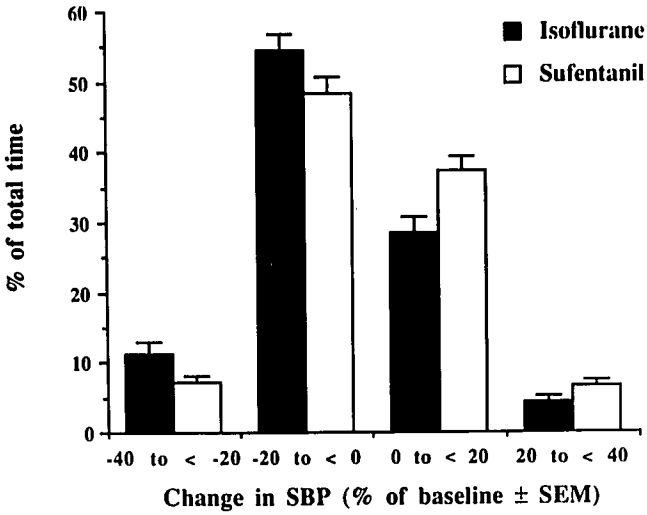

FIG. 2. The frequency distributions of systolic blood pressure (SBP) as percentage changes from preoperative baseline values in 186 patients.

TABLE 2. Characteristics of Prebypass TEE Ischemic Episodes (n = 162)

	Isoflurane	Sufentanil	*P* Value
Patients (%) with TEE episodes	21	20	0.97
Mean duration (min)	21 ± 18	26 ± 25	0.44
Median duration (min)	16	18	0.48
Mean change in WMS	2.5 ± 0.8	2.7 ± 1.5	0.57
Median change in WMS	2	2	0.94
Min ischemia/h monitored	14.3 ± 12.2	13.8 ± 10.9	0.90

WMS = wall-motion score. The wall motion of each of the four segments of the left ventricle at the level of the short axis was graded using a five-point scale (see text). A "TEE episode" suggestive of ischemia was defined by regional wall motion worsening ≥ 2 grades and lasting ≥ 1 min.

no difference between isoflurane (12 of 56 = 21%) and sufentanil anesthesia (21 of 106 = 20%) ($P = 0.97$; 95% CI for the difference = −14 to 12%). The characteristics of TEE episodes did not differ significantly between the two groups (table 2). Of the 46 TEE episodes that were detected, 7 of 17 (41%) of the episodes that were associated with hemodynamic changes occurred in patients receiving isoflurane and 5 of the 29 (17%) occurred in patients receiving sufentanil. Of the 7 hemodynamically related episodes in the isoflurane-treated group, 3 were related to increases (>20%) in HR, 2 were related to decreases in SBP, 1 was related to increases in SBP, and the last was related to increases in HR, SBP, and PAD. Of the 5 episodes in the sufentanil-treated group, 4 episodes were related to increases in HR and the fifth was related to decreases in SBP. Although TEE episodes in the isoflurane-treated group tended to be preceded by acute changes in hemodynamics (*i.e.*, 41% *vs.* 17% of episodes in the sufentanil-treated group), this difference was not significant ($P = 0.15$). No correlation was observed between TEE ischemic episodes and the isoflurane concentrations (range, 0.47–1.75%).

ELECTROCARDIOGRAPHIC EPISODES

Preoperatively, ECG changes suggestive of ischemia developed in 70 of 176 (40%) patients, with no difference between patients who received isoflurane (26 of 59 [44%]) or sufentanil (44 of 117 [38%]) ($P = 0.51$).

Intraoperatively, during the prebypass period, ECG evidence of ischemia developed in 34 of 181 (19%) patients, with no difference between patients who received isoflurane (12 of 59 = 20%) or sufentanil (22 of 122 = 18%) ($P = 0.87$; 95% CI for the difference = −15 to 11%). Of the 34 patients in whom prebypass ECG evidence of ischemia developed, 31 had ST-segment depression. ST-segment elevation developed in 2 other patients, and ST-segment elevation followed by ST-depression developed in the third patient. The characteristics of electrocardiographic ischemic episodes were similar in patients receiving either isoflurane or sufentanil (table 3).

Forty-four of the 176 patients (25%) had only preoperative ischemia, with no difference between patients receiving isoflurane (17 of 59 = 29%) or sufentanil (27 of 117 = 23%) ($P = 0.52$). Eight of the 181 patients (4%) had new ischemia develop in the prebypass period, again with no difference between isoflurane- (3 of 59 = 5%) and sufentanil-treated (5 of 122 = 3%) groups ($P = 0.93$). Contrasting the characteristics of the ischemic episodes in patients in whom electrocardiographic ischemia developed in either the preoperative or prebypass periods, both the mean ST-segment depression and duration were significantly lower in the prebypass period in both the isoflurane- and sufentanil-treated groups (table 4). However, the mean area-under-the-curve and minutes of ischemia/hours monitored were similar in both periods (table 4).

TABLE 3. Characteristics of Prebypass ECG Ischemic Episodes (n = 181)

	Isoflurane	Sufentanil	*P* Value
Patients (%) with ECG episodes	20	18	0.87
Mean ST-depression	−1.6 ± 0.5	−1.6 ± 0.7	0.93
Median ST-depression	−1.5	−1.5	0.86
Mean duration (min)	37.7 ± 22.9	41.3 ± 34.8	0.48
Median duration (min)	32.0	33	0.87
Mean AUC	−45 ± 37.3	−53.2 ± 79.6	0.72
Median AUC	−28.8	−22.5	0.48
Min ischemia/h monitored	20.8	18.2	0.58

AUC = area under the ST-segment-time curve, which provides an estimate of the severity of an ECG ischemic episode.

TABLE 4. Comparison Between Preoperative and Prebypass ECG Ischemic Episodes

	Isoflurane			Sufentanil		
	Preoperative	Prebypass	*P* Value	Preoperative	Prebypass	*P* Value
Mean ST-segment (mm)	−1.6 ± 0.7	−0.7 ± 0.9	0.0009	−1.8 ± 0.9	−0.6 ± 0.9	0.0001
Mean duration (min)	50.3 ± 63.5	15.8 ± 24.1	0.01	38 ± 34.5	19 ± 28.2	0.01
Mean AUC (mm · min)	−72.7 ± 143.2	−17.3 ± 32.9	0.05	−55.9 ± 75.8	−20.2 ± 46.3	0.007
Mean min ischemia/h monitored	5.1 ± 10.7	4.3 ± 10.3	0.62	2.1 ± 5.7	3.1 ± 8.6	0.23

The mean values displayed above are obtained from those patients who developed ECG evidence of ischemia in either the preoperative and/or the prebypass periods. Forty-four patients had preoperative ischemia only; 26 patients had both preoperative and prebypass ischemia; and 8 patients had prebypass ischemia only.

Although electrocardiographic episodes in the isoflurane-treated group tended to be preceded by acute changes in hemodynamics (*i.e.*, 50% *vs.* 35% of episodes in the sufentanil-treated group) this difference was not significant ($P = 0.6$).

Relationship Between TEE and Electrocardiographic Ischemic Episodes

Of the 186 patients studied, 155 have both usable intraoperative TEE and Holter data. Of the 46 TEE episodes detected, 13 of 46 (28%) have corresponding ECG changes. Six of the 13 concordant episodes (46%) occurred in patients who received isoflurane, and 7 of 13 (54%) occurred in patients who received sufentanil.

Of the 41 electrocardiographic episodes detected, 11 of 41 (27%) have corresponding TEE changes. Five of the 11 concordant episodes (45%) occurred in patients who received isoflurane, and 5 of 11 (55%) occurred in patients who received sufentanil.

Relationship to Intraoperative Drugs and Surgical Events

The intraoperative drug data are summarized in table 5. Patients who were randomized to receive isoflurane were given significantly more ephedrine and Neo-Synephrine® (Winthrop Pharmaceuticals, New York, NY) to maintain blood pressure. They also received significantly more fentanyl and sodium thiopental as adjuncts to the primary anesthetic during anesthetic induction. In contrast, patients who were randomized to receive sufentanil were more likely to receive a vasodilator (nitroglycerin) to decrease blood pressure.

The number of grafts, total aortic cross-clamp time and cardiopulmonary bypass time, and surgeon's overall assessment of the grafts were similar in patients receiving isoflurane or sufentanil (table 6).

TABLE 5. Intraoperative Drug Data in 186 Patients

	Isoflurane (n = 62)	Sufentanil (n = 124)	*P* Value
Dopamine	0	1 (1%)	0.71
Ephedrine	26 (42%)	17 (14%)	0.0001
Neosynephrine	46 (74%)	67 (54%)	0.01
Nitroglycerin	11 (18%)	48 (39%)	0.006
Nitroprusside	0	8 (6%)	0.10
Calcium-channel blockers	1 (2%)	1 (1%)	0.80
β-adrenergic blockers	9 (15%)	11 (9%)	0.36
Diazepam	53 (85%)	120 (97%)	0.01
Fentanyl	51 (82%)	0	0.0001
Sodium thiopental	42 (68%)	26 (21%)	0.0001

Relationship to Adverse Outcome

The numbers of patients in whom adverse cardiac outcomes developed are summarized in table 6. There was no significant difference in the incidence of adverse outcome between the groups.

Discussion

Our study demonstrated that the risk of myocardial ischemia during isoflurane and sufentanil anesthesia was similar under conditions of strict hemodynamic control.

Comparison with Previous Studies

The effects of anesthetics on myocardial ischemia have been investigated in animal models and human subjects,

TABLE 6. Surgical and Outcome Data in 186 Patients

	Isoflurane (n = 62)	Sufentanil (n = 124)
Surgical data		
Grafted vessels (number)	3 (1–5)	3 (1–5)
Aortic cross-clamp time (min)	59 ± 17	59 ± 17
Bypass time (min)	102 ± 25	104 ± 32
Surgical assessment		
4 (excellent)	14 (25%)	28 (24%)
3 (good)	25 (45%)	61 (52%)
2 (fair)	15 (27%)	27 (23%)
1 (poor)	1 (2%)	2 (2%)
Outcome data		
Myocardial infarction	3 (5%)	8 (6%)
Ventricular failure	0	4 (3%)
Cardiac death	1 (2%)	3 (2%)
Total outcome	4 (6%)	15 (12%)

with conflicting results. Direct comparison of the results of these studies with ours is difficult because different methods and measures of myocardial ischemia were used. Additionally, no previous study has examined the risk of myocardial ischemia using rigorous hemodynamic controls and continuous measurement of myocardial ischemia.

Animal Data

The administration of isoflurane during critical stenoses in dogs has resulted in regional myocardial dysfunction suggestive of myocardial ischemia.[10] Using a similar model, Tatekawa *et al.* found that the addition of isoflurane significantly reduced the endocardial–epicardial ratio of the stenosed region, although there was no evidence of ischemia.[16] However, in both studies, the administration of isoflurane was accompanied by 20–40% decreases in mean aortic pressure. Because flow distal to a critical stenosis becomes highly pressure-dependent, it is likely that the observed regional myocardial ischemia occurred secondary to a localized decrease in blood supply from a significant reduction in perfusion pressure.

Buffington *et al.* used a dog model of gradual coronary occlusion and collateral-dependent myocardium to study the effects of isoflurane on coronary hemodynamics.[8] They demonstrated that when the collateral-dependent myocardium was made ischemic at rest by decreasing the regional perfusion, the addition of isoflurane redistributed blood flow from the collateral-dependent to the normally perfused area. Redistribution of blood flow from the endocardium to epicardium, as well as a decrease in systolic contraction, also was observed. However, isoflurane did not induce or worsen myocardial ischemia by redistribution except when the area at risk was pressure-dependent. In contrast, coronary steal was not evident after the administration of isoflurane as an adjuvant anesthetic in a chronic dog model.[17]

Other studies have actually shown beneficial effects of isoflurane in experimental models of myocardial ischemia. Gilbert *et al.* demonstrated that isoflurane was associated with a greater coronary reserve and a better preservation of cardiac function than halothane.[18] Warltier *et al.* found that the time course of recovery of function of previously ischemic myocardium was enhanced by isoflurane equally as well as by halothane, using a chronically instrumented dog model.[19] Davis and Sidi demonstrated that isoflurane had no deleterious effect on acute evolving myocardial infarction in the dog and was associated with salvage of myocardium.[20] The cardioprotective effect of isoflurane may involve reducing the severity of ischemia during coronary artery occlusion by decreasing myocardial oxygen demand.

The results of these animal studies therefore suggest that isoflurane can induce myocardial ischemia when coronary perfusion pressure is decreased and that coronary steal may occur when the collateral flow is pressure-dependent.[8] However, absence of deleterious or even beneficial effects from isoflurane administration have also been reported.[17–20] The clinical significance of these findings therefore remains uncertain.

Human Data

Results of human studies of isoflurane's effects on coronary hemodynamics also differ. In 21 patients undergoing major vascular surgery, Reiz *et al.* found a 48% incidence of ECG changes suggestive of ischemia during isoflurane anesthesia, and that patients with electrocardiographic ischemic changes had decreased myocardial lactate extraction but a constant coronary flow even though myocardial oxygen consumption was diminished.[1] Because isoflurane caused coronary vasodilation and because correction of blood pressure did not relieve ischemia in some patients, Reiz *et al.* postulated that isoflurane might be causing ischemia by a "steal" mechanism.

Several subsequent studies also demonstrated either ECG or metabolic evidence of myocardial ischemia in patients under isoflurane anesthesia. Moffitt *et al.* studied 10 patients undergoing CABG surgery and reported that lactate production developed in 3 of 10 patients, which was suggestive of regional or global myocardial ischemia.[12] Khambatta *et al.* reported that, in 20 patients with coronary artery disease undergoing isoflurane or halothane anesthesia,[13] global lactate production and ECG changes developed in 4 of 10 patients receiving isoflurane and changes in regional lactate production developed in 3 patients receiving isoflurane. Additionally, the ratio of regional to global perfusion decreased in those receiving isoflurane and was unchanged in those given halothane. In contrast, all patients receiving halothane had net myocardial lactate extraction. These authors concluded that isoflurane has the propensity to induce maldistribution of the coronary circulation and myocardial ischemia and that halothane is a preferable anesthetic in patients with coronary artery disease.

One limitation to interpreting the results of these clinical studies is that anesthetic induction resulted in a 30–45% decrease in coronary perfusion pressure. Therefore, distinguishing between reductions in coronary perfusion pressure and redistribution of blood flow within the myocardium as the cause of ischemia is difficult. One study did attempt to normalize coronary perfusion pressure by the combined use of phenylephrine, nitroglycerin, and pacing in patients with ECG and metabolic changes; however, three of the five patients had persistent signs of myocardial ischemia.[1] Although the author suggested that the persistent ischemia was secondary to coronary steal, this could not be proven by this study. The use of atrial pacing and phenylephrine in patients who were already ischemic may have deleterious effects on the myocardium.

Isoflurane's beneficial effects on coronary hemodynamics have been demonstrated in two studies. Tarnow *et al.* studied 14 patients scheduled for CABG surgery while they were awake and during 0.5% isoflurane anesthesia with 50% N_2O. ECG evidence of ischemia and/or V-waves in pulmonary capillary wedge pressure occurred at a higher pacing rate during isoflurane anesthesia than in the awake state.[5] O'Young *et al.* found no ECG or metabolic evidence of myocardial ischemia after administration of 0.75–1.0% isoflurane as an adjuvant anesthetic to control intraoperative increases in systemic arterial pressure during sternotomy in patients undergoing CABG surgery.[4] These results also suggest that isoflurane is safe in doses that produce no significant hypotension. When we prospectively and rigorously controlled hemodynamics, we found no difference in the incidence of myocardial ischemia as measured by two sensitive and continuous techniques (ECG and TEE). We also found no difference in the incidence of adverse cardiac outcomes in our patients, although the number of outcomes was small.

In contrast to our findings are the results from a recent study by Inoue *et al.* in patients undergoing elective CABG surgery. These authors reported that the rates of postoperative myocardial infarction were twofold higher and in-hospital deaths were sevenfold higher in patients who received isoflurane than in those who received enflurane.[21] The differences in findings between the two studies are likely attributed to differences in study design. First, in our study, when hemodynamics were controlled rigorously, we were unable to demonstrate a difference in the incidence of myocardial ischemia in patients receiving isoflurane or sufentanil. In the study by Inoue *et al.*, although the authors reported that they attempted to maintain SBP between 110 and 90 mmHg, no data were provided to document the degree of their hemodynamic control. Second, it was possible that the two patient groups in the study of Inoue *et al.* were not equally matched: 1) patients receiving isoflurane had preoperative renal dysfunction more frequently than those receiving enflurane; 2) patients receiving enflurane were more likely to receive nitroglycerin intraoperatively, which may have a protective effect on the myocardium; 3) no data were provided to indicate whether the two different surgical techniques (intermittent aortic cross-clamping with a warm fibrillating heart and continuous aortic cross-clamping) were randomized equally; and 4) the amount of the adjuvant anesthetic, fentanyl, was not provided. Furthermore, the authors indicated that, in case of difficult separation from cardiopulmonary bypass, the anesthesia was actually changed (from enflurane or isoflurane) to intravenous fentanyl and midazolam, making comparison between groups difficult.

In contrast to the study by Inoue *et al.* and in agreement with our findings are two recent prospective outcome studies addressing the issue of anesthetic choice in patients undergoing CABG surgery.[22,23] They demonstrate that isoflurane is not contraindicated in high-risk patients with coronary disease undergoing CABG surgery and support the hypothesis that anesthetic choice has little bearing on outcome in patients with coronary artery disease. Specifically, no deleterious effects occurred when isoflurane was used as a primary or secondary anesthetic in patients in either of these studies. Although the current study does not include at-risk patients undergoing noncardiac procedures, it is likely that isoflurane also can be used in these patients because they have underlying cardiac risk factors similar to those in our patients.

Clinical Implications

Our results demonstrate that it is as safe to use isoflurane as sufentanil in high-risk patients when hemodynamics are rigorously controlled. In addition, the current results support our previous report of the prevalence of myocardial ischemia in the preoperative period as measured by ambulatory Holter ECG.[24,25] This ischemic pattern is no worse intraoperatively, and, in fact, the magnitude and duration were suppressed equally well by both isoflurane and sufentanil when hemodynamics are controlled. The myocardial protective effects of anesthetics may involve decreases in myocardial oxygen demand.

Limitations

Several potential limitations exist in this current study. First, we recognize that because there is not an absolute reference standard for measuring myocardial ischemia, validating TEE regional wall motion abnormalities (RWMA) or ECG ST changes is difficult. However, RWMA have been shown to be sensitive and early markers of myocardial ischemia by a number of experimental and clinical studies in animals and humans.[26–34] Our work and that of others have indirectly shown that RWMA detected intraoperatively are likely to be ischemic in origin.[15,35] Similarly, although there are nonischemic causes for ST-segment changes, such as ventricular hypertrophy, altered electrical activity, changes in body temperature, changes in serum electrolytes, ventilatory changes or administration of drugs, most of these changes are usually chronic conditions and not acutely reversible (our definition of electrocardiographic ischemia requires reversible ST-segment changes). Therefore, reversible ST-segment changes are likely to be ischemic. Furthermore, the strong relationship observed between ST-segment abnormalities and the subsequent development of adverse cardiac outcomes suggests the predictive validity of ST abnormalities.[25]

Second, when isoflurane was used as a primary anesthetic, additional adjuvant drugs, including sodium thiopental, fentanyl, and diazepam, were allowed to be administered during anesthetic induction. These agents may have independent or synergistic effects on cardiac per-

formance. However, a "balanced technique" with isoflurane as the primary anesthetic is a more likely technique to be used clinically. The results from this study can therefore be generalized to the larger class of patients with coronary artery disease undergoing general anesthesia with isoflurane as the primary anesthetic.

Third, the intraoperative use of nitroglycerin in controlling blood pressure may potentially confound our results on ischemic measurement. However, additional examination of the results reveals that the incidence of either TEE or electrocardiographic ischemia was not different between patients who were receiving nitroglycerin and those who were not. In the 162 patients who had interpretable TEE data, 35 patients received nitroglycerin and 10 of 35 patients (29%) had TEE evidence of ischemia. In contrast, of the 127 patients who did not receive nitroglycerin, 41 of 127 (32%) had TEE evidence of ischemia ($P = 0.83$). Similarly, in the 181 patients who had interpretable ECG data, 34 patients received nitroglycerin. Twelve of the 34 patients (35%) had ECG evidence of ischemia. Of the 147 patients who did not receive nitroglycerin, 46 of 147 (31%) had ECG evidence of ischemia ($P = 0.81$).

In addition, because significantly more ephedrine and Neo-Synephrine® were administered to patients receiving isoflurane than sufentanil, one could argue that these agents may have a direct effect on the coronary vasculature. If Neo-Synephrine® or ephedrine did play a role in causing coronary vasoconstriction, then the incidence of myocardial ischemia in the isoflurane-treated group might have been lower if these agents were not used, further supporting our data that isoflurane is safe.

Fourth, it has been suggested that isoflurane is not a potent coronary vasodilator and that only a subset of patients with "steal-prone" coronary anatomy (total occlusion of at least one major coronary artery, and a concomitant hemodynamically significant stenosis of the collateral-supplying vessel) are likely to be susceptible to the development of coronary steal.[36] Although the current report has not specifically addressed this issue, the coronary anatomy of all the studied patients will be stratified in a future report to examine whether intraoperative myocardial ischemia is more likely to develop in those with a "steal-prone anatomy" while they are under isoflurane anesthesia.

Fifth, although the ischemic episodes (TEE or ECG) in the isoflurane-treated group tended to be more frequently preceded by acute changes in hemodynamics than in the sufentanil-treated group, we were unable to demonstrate a statistically significant difference, probably because the number of ischemic episodes was small in our study. However, one could argue that if hemodynamics were even "better controlled" in the isoflurane-treated group, the incidence of ischemia might have been even lower.

Finally, one could argue that our sample size may not be sufficient for detection of a difference between groups. Although we observed no difference in the proportion of patients in whom ischemia (TEE or ECG) developed in the two groups ($P = 0.97$ and $P = 0.87$), we cannot exclude the possibility of a small difference in ischemia between the two anesthetics.

In conclusion, our study demonstrates that, under strict hemodynamic control, isoflurane anesthesia was associated with an incidence of myocardial ischemia (TEE or ECG) similar to that of sufentanil anesthesia. Furthermore, both the magnitude and duration of electrocardiographic ischemia appeared to be blunted during the prebypass period compared with those in the preoperative period, and to be blunted equally well by both anesthetics. These results also suggest that, under conditions of strict hemodynamic control, anesthetics may have a protective effect on the myocardium at risk.

The authors thank staff anesthesiologists (Robert Hickey, M.D., Martin London, M.D.) and surgeons (Edward Verrier, M.D., Fraser Keith, M.D., Scott Merrick, M.D.) for their cooperation and support in making this study possible. They also thank the anesthesia residents from Letterman Army Medical Center, San Francisco (Eric Helander, M.D., James Helman, M.D., Joseph Scaniffe, M.D., Mark Woiwood, M.D.) for their participation, and Warren Browner, M.D., for statistical advice.

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Appendix

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