Anesthesiology
77:47–62, 1992

The Risk of Myocardial Ischemia in Patients Receiving Desflurane versus *Sufentanil Anesthesia for Coronary Artery Bypass Graft Surgery*

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Desflurane, a coronary vasodilator, may induce myocardial ischemia in patients with coronary artery disease. To determine whether desflurane is safe to administer to the at-risk patient population (with known coronary artery disease), we compared the incidence and characteristics of perioperative myocardial ischemia in 200 patients undergoing coronary artery bypass graft (CABG) surgery randomly assigned to receive desflurane (thiopental adjuvant) *versus* sufentanil anesthesia. Under conditions of hemodynamic control, perioperative ischemia was assessed using continuous echocardiography (precordial: during induction; transesophageal: during surgery) and Holter electrocardiography (ECG); hemodynamics (including pulmonary artery pressure) were measured continuously. *Hemodynamic results:* During induction, no significant changes in hemodynamics occurred in the sufentanil group, while in the desflurane group, heart rate, systemic and pulmonary arterial pressure increased and stroke volume decreased significantly. During the intraoperative period, the incidence of hemodynamic variations was low in both anesthetic groups; however, the prebypass incidence of tachycardia (>120% of preoperative baseline heart rate) was greater in the desflurane group (4 ± 7% of total time monitored) than in the sufentanil group (1 ± 6%) ($P = 0.0003$). Similarly, the incidence of prebypass hypotension (< 80% of preoperative baseline systolic arterial blood pressure) was greater in the desflurane group (21 ± 14%) than in the sufentanil group (15 ± 16%) ($P = 0.01$). *ECG results:* Preoperatively, 15% (28/191) of patients developed ECG ischemia, with no difference between patients who received desflurane, 13% (12/96) or sufentanil, 16% (16/95) ($P = 0.6$). During anesthetic induction, 9% (9/99) of patients who received desflurane developed ECG ischemia, compared with 0% (0/98) who received sufentanil ($P = 0.007$). During the prebypass period, 5% (10/197) of patients developed ECG ischemia, with no difference between patients who received desflurane, 7% (7/99) or sufentanil, 3% (3/98) ($P = 0.3$). Postbypass, 12% (24/194) of patients developed ECG ischemic changes, with no difference between patients who received desflurane, 13% (13/97) or sufentanil, 11% (11/96) ($P = 0.9$). *Echocardiographic results:* The incidence of precordial echocardiographic ischemia during anesthetic induction was 13% (5/39) in the desflurane group *versus* 0% (0/29) in the sufentanil group ($P = 0.1$). Moderate to severe transesophageal echocardiographic (TEE) ischemic episodes occurred in 12% (21/175) of patients during prebypass, with no significant difference between the desflurane group, 16% (15/91) and the sufentanil group, 7% (6/84) ($P = 0.09$). TEE ischemic episodes occurred in 27% (49/178) of patients during the postbypass period, with no difference between the desflurane, 29% (27/92) and sufentanil, 25% (22/86) groups ($P = 0.7$). *Adverse outcomes:* The incidence of adverse cardiac outcome did not differ between anesthetic techniques (desflurane 6%, sufentanil 7%). During maintenance of anesthesia, the risk of myocardial ischemia was not significantly increased with desflurane *versus* sufentanil anesthesia when hemodynamics were tightly controlled. However, during induction of anesthesia, desflurane (when used without adjuvants except for thiopental) was associated with more hemodynamic changes and myocardial ischemia, compared with sufentanil. (Key words: Anesthesia: cardiac. Anesthetics, intravenous: sufentanil. Anesthetics, volatile: desflurane. Heart: coronary artery disease; myocardial ischemia. Monitoring: blood pressure; hemodynamics; Holter electrocardiography; precordial echocardiography; pulse rate; transesophageal echocardiography. Surgery: coronary artery bypass graft.)

CORONARY ARTERY DISEASE is the most common disease state among patients presenting for surgery. The incidence of perioperative myocardial ischemia in patients at risk for coronary artery disease is high, ranging from 18 to 74% of noncardiac surgical patients[1–5] and 20 to 55% in cardiac surgical patients.[6–16] Because perioperative myocardial ischemia may be related to postoperative myocardial infarction, limiting intraoperative myocardial ischemia is an important anesthetic consideration.[17]

The new volatile anesthetic, desflurane, has a low blood solubility, suggesting that it may be particularly useful for rapid induction as well as rapid emergence and recovery.[18] Because of these characteristics, desflurane is likely to be used in patients undergoing noncardiac surgery where rapid emergence and recovery is desirable. However, because 7 of 25 million patients presenting for noncardiac surgery annually have or are at risk for coronary artery disease, proving that desflurane is safe in this patient population is critical.[19]

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We chose patients undergoing coronary artery bypass graft (CABG) surgery as study subjects because they have well defined coronary artery anatomy and are extensively instrumented for clinical purposes, facilitating continuous hemodynamic data measurements. Our study goal was to determine whether desflurane should be restricted in patients with coronary artery disease. Our hypothesis is that desflurane is not associated with an increased incidence of myocardial ischemia under conditions of rigorous hemodynamic control. We compared the risk of myocardial ischemia during desflurane *versus* sufentanil anesthesia using continuous echocardiography and Holter electrocardiography (ECG) and continuous hemodynamic measurements, under conditions of hemodynamic control.

Materials and Methods

We prospectively studied 200 patients scheduled for elective CABG surgery from August 1990 to April 1991 at the San Francisco Kaiser Permanente Medical Center, after obtaining their informed consent and the approval of the committees on human research of the University of California, San Francisco and Kaiser Permanente, San Francisco. Demographic and clinical data obtained for each patient included any history of prior myocardial infarction, previous CABG surgery or angioplasty, unstable angina, hypertension, diabetes mellitus, and preoperative medications. We included only patients with ejection fraction > 30% and identified significant coronary-arterial stenoses as those ≥ 70% diameter of the left anterior descending, left circumflex, or right coronary artery or ≥ 50% diameter of the left main coronary artery. Patients with uninterpretable preoperative (ward) ECGs (pacemaker, left bundle branch block) or esophageal disease precluding the insertion of the transesophageal echocardiographic (TEE) probe were excluded from study.

Anesthetic Management

Patients were randomly allocated to groups that were to receive either desflurane or sufentanil for induction and maintenance of anesthesia. All patients received midazolam (up to 0.1 mg/kg intramuscularly) and morphine sulfate (0.1–0.2 mg/kg intramuscularly) 60–90 min prior to surgery and continued to receive their chronic oral cardiac medications. Routine intraoperative monitoring included ECG (leads II and V5), pulse oximetry, radial and pulmonary artery catheterization, mass spectrometry (capnography, anesthesia agent), and pulmonary artery temperature.

Before administering either anesthetic agent, all patients breathed 100% oxygen by mask for 5 min and then received up to 0.1 mg/kg midazolam and up to 7 mg/kg sodium thiopental, intravenously. In the desflurane group, anesthesia was induced using 1.0–2.0 MAC end-tidal concentration (ET) of desflurane in oxygen *via* controlled ventilation by mask for 15 min and was maintained at 1.0 MAC (ET) after tracheal intubation. Desflurane was administered from a modified Ohio DM 5000 anesthesia machine (Ohmeda, Madison, WI) with an electrically heated, temperature-controlled pressurized vaporizer. Sufentanil anesthesia was induced using an intravenous bolus of sufentanil, 5–10 μg/kg, administered over 10 min and maintained using a continuous infusion of 0.07 $\mu g \cdot kg \cdot^{-1} \cdot min^{-1}$ during the prebypass period. In both groups, vecuronium 0.1–0.2 mg/kg was administered immediately after the thiopental to facilitate tracheal intubation. Pancuronium was administered to facilitate tracheal intubation at the discretion of the clinician in patients with heart rates < 50 beats/min prior to the induction of anesthesia. All patients received 100% inspired oxygen to maintain Pa_{O_2} > 70 mmHg. Ventilation was controlled (tidal volume 10–15 ml/kg) to maintain Pa_{CO_2} between 35 and 45 mmHg. Pulmonary artery temperatures were maintained between 35.0 and 37.5° C during the prebypass period.

Anesthesiologists were requested to maintain heart rate within <120% and systolic blood pressure (SBP) within ±20% of preoperative baseline values (derived from the mean of ward measurements from the 24 h prior to surgery) throughout the prebypass period. If the hemodynamic values exceeded the baseline variables, the inspired concentration of desflurane was increased in the desflurane group, and an intravenous bolus of 1 μg/kg sufentanil was administered to the sufentanil group, followed by an increase in the sufentanil infusion rate of 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$. A maximum of three such increases was permitted before adjunctive treatment. Persistent (≥2 min in duration) hypertension or tachycardia (>120% of control SBP or heart rate, respectively) in either group was treated with a vasodilator (sodium nitroprusside) or a β-adrenergic blocking agent (esmolol), respectively. Hypotension (<80% of control SBP) in the desflurane group was treated by reducing the fractional inspired desflurane concentration and, in both groups, by administration of intravenous fluids and/or vasopressors.

At the onset of cardiopulmonary bypass, the desflurane group received an intravenous bolus of 1 $\mu g \cdot kg \cdot^{-1}$ sufentanil and both patient groups received an infusion of 0.01 $\mu g \cdot kg \cdot^{-1} \cdot min^{-1}$. During bypass, midazolam (up to 0.2 mg/kg) was administered to both groups to provide amnesia. Anesthesiologists were requested to maintain the mean arterial pressure (MAP) between 30 and 100 mmHg. If the MAP exceeded 100 mmHg, an intravenous bolus of 1 μg/kg sufentanil was administered to the sufentanil group, followed by an increase in the sufentanil infusion rate of 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$. A maximum of three such increases was permitted before adjunctive treatment. Persistent (≥ 2 min) hypertension (MAP > 100 mmHg) or hypotension (MAP < 30 mmHg) in either

group was treated with a vasodilator (sodium nitroprusside) or phenylephrine, respectively.

Following bypass, the sufentanil infusion was discontinued in the desflurane group, and anesthesia was maintained with 1.0 MAC (ET) desflurane in oxygen. In the sufentanil group, the infusion was increased to 0.015 $\mu g \cdot kg \cdot^{-1} \cdot min^{-1}$. The anesthesiologists were requested to maintain the heart rate < 110 beats/min and SBP > 90 mmHg throughout the postbypass period. If the hemodynamic values exceeded the prescribed parameters, the inspired concentration of desflurane was increased in the desflurane group, and an intravenous bolus of 1 $\mu g/kg$ sufentanil was administered to the sufentanil group, followed by an increase in the sufentanil infusion rate of 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$. A maximum of three such increases was permitted before adjunctive treatment. Persistent (≥ 2 min) hypertension (>120% of control SBP) or tachycardia (>110 beats/min) in either group was treated with a vasodilator (sodium nitroprusside) or a β-adrenergic blocking agent (esmolol), respectively. Hypotension (<90 mmHg) in the desflurane group was treated by reducing the fractional inspired desflurane concentration and, in both groups, by administration of intravenous fluids and/or vasopressors. Intraoperative administration of therapeutic drugs was recorded.

Surgical Management

Cardiopulmonary bypass was performed using a membrane oxygenator, hemodilution, and moderate systemic hypothermia (25–28° C). Multidose cold crystalloid cardioplegia (5° C) with potassium (20 mEq/l) and topical saline ice slush were used for myocardial protection during bypass. Distal anastomoses were performed during continuous aortic cross-clamping, followed by proximal vein grafting during partial aortic occlusion. One-hundred ninety subjects received vein grafts, and 178 subjects received internal mammary artery grafts to either the left anterior descending or the first diagonal coronary artery. The pericardium was left open in all subjects. The quality of the bypass grafts was assessed by the surgeons, who were unaware of the echocardiographic, specialized ECG, and hemodynamic findings. The grafts were graded qualitatively as poor (1), fair (2), very good (3), and excellent (4).

Intraoperative Measurements

Hemodynamics

Intraoperatively, we continuously recorded the SBP, MAP, and diastolic arterial blood pressure (DBP); systolic, mean, and diastolic pulmonary artery pressures; and heart rate on a Hewlett-Packard Merlin component monitoring system (M 1046-9001B). The zero reference point was located 5 cm posterior to the sternal angle in a direction perpendicular to the frontal plane of the chest. Hemodynamic data were averaged every 60 s and stored by the computer. All hemodynamic data also were recorded onto hard copy at 10 mm/min with an eight-channel strip-chart recorder (Graphtec) linked to the hemodynamic monitor. The time clocks on the echocardiographic and Holter monitors and the hemodynamic recorder were synchronized before anesthetic induction. The data on the hard copy were reviewed to ensure that artifacts (such as erroneous values resulting from blood drawings or flushing of catheters) were excluded from analysis, then entered into a computer spreadsheet (SAS Institue, Cary, NC) for each patient. Data were then analyzed for any relationship between acute hemodynamic change and ischemic episodes. Acute hemodynamic change was defined as an increase (> 120% of baseline) in heart rate, SBP, or pulmonary artery diastolic pressure, or a decrease in DBP to < 80% of baseline at 5 and 10 min preceding the onset of an ischemic episode.

Electrocardiography

ECG monitoring was performed using a two-channel AM Holter ECG recorder (Marquette Electronics, series 8500) the day before surgery (baseline), intraoperatively, and postoperatively for 48 h. 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. Before study, the effect of positional variation on ECG morphology was measured in the supine, left lateral decubitus, right lateral decubitus, and upright positions. Each complete ECG recording on Holter tape was scanned visually using an ECG analysis system (Marquette, series 8000). All abnormal 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. ECG episodes of ischemia were defined as reversible ST-segment changes lasting at least 1 min and involving a shift from baseline (adjusting for preoperative positional changes) of either ≥ 1 mm of ST depression (J + 60 ms) or ≥ 2 mm of ST elevation (J-point). ST-segment depression was measured 60 ms after the J-point, unless that point fell within the T wave, in which case it was measured at a minimum of J + 40 ms. The baseline ST-segment level was defined as the average ST segment during a stable period (usually 15–60 min) preceding each episode, and the maximum ST change from baseline was determined for each episode. The reversibility of an ischemic episode was defined by the return of the ST segment to baseline for at least 1 min. ECG characteristics analyzed were: 1) maximum change in the ST segment, 2) episode duration, 3) area-under-the-curve (integral of the change in ST segment over time), and 4) episode duration relative to du-

ration of the monitoring period (*e.g.*, prebypass period). All possible ECG ischemic episodes were reviewed and verified by two investigators who were blinded to patient identity and outcome.

Echocardiography

Precordial (transthoracic) echocardiography was performed during the induction period to assess left ventricular function and potential wall-motion changes suggestive of ischemia or depression of myocardial contractility. Immediately following the application of the face mask for preoxygenation, a 2.5-MHz phased array transducer (Hewlett-Packard) was positioned on the left hemithorax (patient in the supine position) and maintained at the level of the midpapillary muscles to obtain a short-axis view of the left ventricle. Precordial data were recorded continuously onto videotapes from the initiation of preoxygenation to 1 min after tracheal intubation. Precordial echocardiographic samples of 60 s duration were obtained at the beginning of preoxygenation (baseline), the completion of induction (preintubation), and immediately after tracheal intubation.

TEE was performed immediately after tracheal intubation. A gastroscope tipped with a 5-MHz phased array transducer (Hewlett-Packard) was introduced into the esophagus, and the transducer was positioned and maintained at the level of the mid-papillary muscles to obtain a short-axis view of the left ventricle. TEE data were recorded continuously onto videotapes during the prebypass period, *i.e.*, from the completion of tracheal intubation to the onset of cardiopulmonary bypass. TEE samples of 60 s duration were obtained from the videotape every 15 min throughout the prebypass period for off-line analysis. To evaluate whether anesthetic or surgically imposed stresses had any immediate effect on regional wall motion, additional TEE samples of 60 s duration were obtained from the videotape immediately after tracheal intubation and at 4 min before and 1 and 6 min after skin incision, sternotomy, pericardiotomy, and aortic and right atrial cannulation for off-line analysis. Postbypass, after completion of the last proximal graft insertion (*i.e.*, release of the aortic side-biting clamp), TEE samples were obtained every 5 min until 1 h after bypass, and then every 15 min until skin closure. Each patient's best prebypass image was used as baseline.

With both echocardiographic techniques, the short-axis, cross-sectional image was divided into four segments using 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 analyzed visually by two investigators, by consensus, who were blinded to patient identity, clinical outcome, time of echocardiographic sampling, and results of ECG analysis. The wall motion of each of the four segments was graded as follows: 0 = normal, 1 = mild hypokinesia, 2 = severe hypokinesia, 3 = akinesia, and 4 = dyskinesia. A segment was considered to contract normally if an imaginary radius to the center of the left ventricle shortened by more than 30% and the wall thickened considerably. Mild hypokinesia was considered to occur if shortening of the radius was less than 30% but more than 10% and the wall thickened. Severe hypokinesia was diagnosed if the wall thickened minimally and radial shortening was less than 10%. An akinetic segment was defined as one in which the wall did not thicken during systole, and a dyskinetic segment as one in which the wall bulged and thinned during systole. This analysis system is qualitative, and the estimates of endocardial motion and myocardial thickening are made by visual inspection in real time and slow motion. An ischemic episode was defined by regional wall motion worsening $\geq$ two grades and lasting $\geq$ 1 min.

To determine the change in wall-motion score over the induction period, a mean wall-motion score was determined for each precordial sample by dividing the sum of the wall-motion scores of all interpretable segments by the number of usable segments. In patients in whom the entire endocardium was visualized, the end-systolic area (ESA) and end-diastolic area (EDA) were derived from precordial images of the left ventricular short-axis view obtained at the beginning of preoxygenation (baseline), the completion of induction (preintubation), and immediately after tracheal intubation. Ejection fraction area (EFA) was calculated using the equation, EFA (percent) = EDA − ESA/EDA × 100. To determine the change in EFA during induction, we compared the EFA values obtained at each measurement interval. The mean duration of all echocardiographic ischemic episodes was determined by measuring episode duration alone and relative to the duration of the monitoring period (*e.g.*, prebypass period).

Interexamination variability was determined by reanalysis after 6 months of a randomly selected 10% of echocardiograms. A discrepancy between observations was defined as a difference of two or more in the scoring of each segment. The degree of interexamination variability was 3%.

Outcome Measurements

A 12-lead ECG was obtained preoperatively (control), daily for the first 3 postoperative days, at discharge from the hospital, and when clinically indicated (chest pain, ECG changes suggestive of ischemia, pulmonary congestion). Serum levels of the MB isoenzyme fraction of cre-

atine phosphokinase were obtained preoperatively (control), every 8 h for the first 2 postoperative days, and when clinically indicated thereafter. Adverse major outcomes were classified, from most to least severe, as: cardiac death; myocardial infarction, and ventricular failure. Cardiac death was defined as mortality during hospitalization attributable to myocardial infarction, dysrhythmia, or heart failure due to a cardiac condition. Myocardial infarction was identified by new Q waves (>40 ms, 25% R wave) on 12-lead ECG *and* creatine phosphokinase MB isoenzyme level > 50 U/l; ventricular failure was defined as cardiac index < 2 $l \cdot min^{-1} \cdot m^{-2}$ and requirement for an intraaortic balloon pump.

Data Analysis

Data are expressed as mean values ± standard deviation (SD), unless otherwise noted. Chi-square analysis with continuity correction was applied to categorical data. Student's *t* test or Mann-Whitney U test was used to test the difference between continuous variables. A *P* value of < 0.05 (two-sided) identified significant differences. The percent change in hemodynamic variables during induction was determined by subtracting baseline values from the values obtained at the completion of induction and immediately after intubation and then applying the following equation: I − B/B × 100, where I = induction (or intubation) and B = baseline.

Results

The two anesthetic groups were similar in size, demographic data, and preoperative medications (table 1). The mean (±SD) end-tidal desflurane concentration during induction was 10.2 ± 2.9% (range of peak induction concentrations: 5.2%–16.4%), and during prebypass, 4.8 ± 1.1%, and postbypass, 2.1 ± 1.0%. The mean end-tidal carbon dioxide (±SD) concentration during induction was 29 ± 6 mmHg in the desflurane group and 32 ± 3 mmHg in the sufentanil group and was similar in both groups during the prebypass (desflurane, 30 ± 4 mmHg and sufentanil, 32 ± 3 mmHg) and postbypass (desflurane, 31 ± 4 mmHg and sufentanil, 31 ± 3 mmHg) periods. The anesthetic agents and muscle relaxants and their respective doses are noted in table 2.

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 either anesthetic (table 3). The mean time to extubation was similar in both groups (desflurane, 19 ± 28 h and sufentanil, 21 ± 23 h).

TABLE 1. Demographics

	Desflurane (n = 100)		Sufentanil (n = 100)	
Sex				
Male	88	88%	84	84%
Female	12	12%	16	16%
Age (yr)	63 ± 9	(38–83)	63 ± 9	(43–82)
Weight (kg)	81 ± 15		82 ± 14	
Unstable angina	28	28%	23	23%
Prior MI	37	37%	42	42%
Months *status post* last MI	59 ± 63		44 ± 51	
Prior CABG	8	8%	8	8%
Prior PTCA	4	4%	5	5%
Hypertension	43	43%	42	42%
Diabetes mellitus	26	26%	21	21%
Hyperlipidemia	35	35%	35	35%
Tobacco use	69	69%	68	68%
Preoperative medications				
Nitrates	71	71%	77	77%
β-Blockers	49	49%	47	47%
Calcium-channel blockers	72	72%	71	71%
Digoxin	7	7%	9	9%
Catheterization data				
Ejection fraction	60 ± 14	(30–88)	58 ± 13	(31–88)
Steal-prone anatomy	24 (90)	27%	26 (91)	28%
Left main disease ≥ 50%	12 (97)	12%	15 (98)	15%
Diseased vessels				
1	5	5%	6	6%
2	21	21%	24	24%
3	74	74%	70	70%

All continuous data are expressed as mean and ±SD when appropriate. For continuous data, the ranges are provided.

MI = myocardial infarction; CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty.

TABLE 2. Intraoperative Drugs in 200 Patients (Desflurane n = 100, Sufentanil n = 100)

Drugs	Induction		Pre-CPB		CPB		Post-CPB	
	Desflurane	Sufentanil	Desflurane	Sufentanil	Desflurane	Sufentanil	Desflurane	Sufentanil
Desflurane (% ET)	10.2 ± 2.9	0	4.8 ± 1.1	0	N/A		2.1 ± 1.0	0
Sufentanil (μg/kg)	0	8.7 ± 1.6*	0	6.0 ± 2.5*	3.7 ± 2.0	2.7 ± 2.1†	0	1.5 ± 0.8*
Midazolam (mg/kg)	0.05 ± 0.04	0.05 ± 0.03	0.01 ± 0.03	0.02 ± 0.03‡	0.07 ± 0.04	0.05 ± 0.04§	0.04 ± 0.03	0.04 ± 0.05
Thiopental (mg/kg)	3.4 ± 1.2	0.8 ± 1.3*						
Vecuronium (mg/kg)	0.2 ± 0.07	0.2 ± 0.07	0.1 ± 0.04	0.1 ± 0.04	0.1 ± 0.08	0.1 ± 0.08	0.02 ± 0.04	0.01 ± 0.03
Pancuronium (mg/kg)	0	0.01 ± 0.03¶			0	0.01 ± 0.03**	0	0.2 ± 1.0

All data are expressed as mean ± SD.
CPB = cardiopulmonary bypass. Induction: arrival in operating room to 5 min after intubation; pre-CPB: 5 min after intubation to CPB.
* $P < 0.0001$ between groups.
† $P < 0.0005$ between groups.
‡ $P < 0.002$ between groups.
§ $P < 0.005$ between groups.
¶ $P < 0.021$ between groups.
** $P < 0.014$ between groups.

INDUCTION OF ANESTHESIA

Perioperative Adjuvant Agents

Significantly more patients given desflurane than given sufentanil required esmolol to treat tachycardia (> 120% of baseline heart rate) (table 4). The number of patients who received nitroglycerin to treat increased pulmonary artery pressure (> 50% increase from baseline) or ECG ST-segment depression was similar in the desflurane group (n = 7) and the sufentanil group (n = 3). Desflurane patients received significantly more sodium thiopental as an adjunct to the primary anesthetic during induction, but the percent change in heart rate in this group did not differ significantly from that in the sufentanil group (median percent change with desflurane = 1% [range −12 to +64%] and with sufentanil = 0% [range −12 to +12%)]. In contrast, a significantly greater number of patients in the sufentanil group required ephedrine and phenylephrine for treatment of bradycardia and/or hypotension to maintain hemodynamic control within the prescribed ranges.

The use of nitroglycerin during induction to treat increased pulmonary artery pressures and/or changes in ST-segment or T-wave morphology may have confounded our detection of the incidence and magnitude of ischemic episodes. However, the incidence of ECG ischemia in patients who were not given nitroglycerin during induction of anesthesia was low (and similar) in patients who received desflurane (n = 91) and those given sufentanil (n = 97) (7% *vs.* 0%, respectively). In addition, the severity of ECG ischemia was similar in desflurane patients who did or did not receive nitroglycerin during induction.

TABLE 3. Surgical Data

	Desflurane		Sufentanil	
	Number	%	Number	%
Aortic cross-clamp (min)	51 ± 16		53 ± 16	
Cardiopulmonary bypass (min)	102 ± 31		101 ± 27	
Bypass grafts performed				
1	6	6	2	2
2	12	12	20	20
3	44	44	39	39
4	34	34	32	32
5	4	4	7	7
Graft choice				
Internal mammary artery + vein	84	84	84	84
Internal mammary artery	7	7	3	3
Vein	9	9	13	13
Surgeon's assessment				
1 = Poor	1	1	2	2
2 = Fair	3	3	4	4
3 = Good	36	36	46	46
4 = Excellent	60	60	48	48

All data are expressed as mean and ±SD as appropriate.

Hemodynamics

Hemodynamic indices were similar in the two anesthetic groups following pulmonary artery catheterization and preceding induction of anesthesia (baseline) (table 5). During induction and intubation, there were small decreases in systemic blood pressure and heart rates and small increases in pulmonary artery blood pressure in the sufentanil group. In contrast, in the desflurane group, heart rate and systemic and pulmonary arterial pressures increased and stroke volume decreased significantly at the completion of induction and after intubation of the trachea. In fact, the rate–pressure product increased significantly in the desflurane group during anesthetic induction even prior to airway instrumentation (table 5). In addition, no evidence of hypoxia, hypercapnia, or airway obstruction was detected during anesthetic induction.

Myocardial Ischemia: Electrocardiography

Interpretable Holter data were obtained in 191 patients during the preoperative period and 197 patients during the induction period (table 6). Preoperatively, 15% (28/191) of patients developed ECG changes suggestive of ischemia, with no difference between patients who re-

TABLE 4. Adjunct Medications in 200 Patients (Desflurane n = 100, Sufentanil = 100)

	Induction		Pre-CPB		CPB		Post-CPB	
Drugs	Desflurane	Sufentanil	Desflurane	Sufentanil	Desflurane	Sufentanil	Desflurane	Sufentanil
Calcium			3%	0%	9%	12%	66%	57%
Calcium-channel blocker					0%	1%	1%	0%
Dobutamine			2%	0%	3%	1%	6%	5%
Dopamine			0%	1%	0%	1%	1%	5%
Ephedrine	1%	26%*	26%	16%	5%	5%	21%	13%
Epinephrine			2%	0%	3%	1%	5%	7%
Esmolol	56%	0%*	32%	3%*	3%	1%	1%	0%
Phenylephrine	27%	43%†	69%	51%‡	60%	45%	40%	22%§
Nitroglycerin	7%	3%	24%	8%¶	16%	7%	27%	25%
Nitroprusside	4%	0%	8%	6%	1%	12%¶	3%	15%**
Norepinephrine					3%	0%	3%	0%

CPB = cardiopulmonary bypass. Induction: preoxygenation to 5 min after intubation; pre-CPB: 5 min after intubation to CPB.
* $P < 0.0001$ between groups.
† $P < 0.018$ between groups.
‡ $P < 0.009$ between groups.
§ $P < 0.0006$ between groups.
¶ $P < 0.002$ between groups.
** $P < 0.003$ between groups.

ceived desflurane 13% (12/96) or sufentanil 16% (16/95) ($P = 0.6$). ST-segment maximum change, episode duration, and area under the curve of preoperative ECG ischemic episodes were similar in both groups. During anesthetic induction, 9% (9/99) of patients who received desflurane developed ECG changes suggestive of ischemia, compared with 0% (0/98) who received sufentanil ($P = 0.007$). In 33% (3/9) of episodes, induction ECG ischemic episodes were preceded by acute hemodynamic changes (increase in heart rate, SBP, pulmonary artery diastolic pressure > 120% of baseline or a decrease in DBP to < 80% of baseline at 5 and 10 min preceding the onset of the ischemic episodes). Two (22%) of the 9 desflurane patients who developed ischemia during induction also had preoperative ECG ischemia.

Myocardial Ischemia: Echocardiography

One hundred twenty of the 200 patients were monitored using precordial echocardiography. Interpretable echocardiographic data were obtained in 68/120 patients (39 in the desflurane group and 29 in the sufentanil group). Moderate to severe ischemic episodes (grade change ≥ 2) occurred in 7% (5/68) of patients during induction. The incidence of induction ischemic episodes was 13% (5/39) in the desflurane group and 0% (0/29) in the sufentanil group ($P = 0.1$).

Examination of all interpretable precordial echocardiographic samples revealed a baseline mean wall-motion score (±SD) of 0.1 ± 0.4 for desflurane patients and 0.3 ± 0.5 for sufentanil patients. Mean wall motion worsened significantly from baseline to induction in desflurane patients (Δ0.3 ± 0.5) compared with sufentanil patients (Δ0.01 ± 0.1) ($P = 0.005$), as well as from baseline to intubation (Δ0.4 ± 0.5 in desflurane patients *vs.* Δ0.03 ± 0.1 in sufentanil patients) ($P = 0.006$). The percent EFA (±SD) at baseline was similar in the desflurane (52 ± 10%) and sufentanil (55 ± 11%) groups. The mean change in EFA from baseline to induction was significantly greater in desflurane patients (Δ−12 ± 10%) than in sufentanil patients (Δ−0.6 ± 6%) ($P = 0.0002$), as was the EFA mean change from baseline to intubation (Δ−12 ± 11% in desflurane patients *vs.* Δ0.1 ± 6% in sufentanil patients) ($P = 0.0005$). Acute hemodynamic changes preceded all precordial ischemic episodes (5/5).

MAINTENANCE OF ANESTHESIA

Perioperative Adjuvant Agents

During the prebypass period, the desflurane anesthetic technique required a significantly greater number of adjunctive medication maneuvers than did the sufentanil technique, as measured by the number of interventions per patient in each group (desflurane = 3 ± 3 maneuvers per patient *vs.* sufentanil = 2 ± 2 maneuvers per patient; $P = 0.0001$). Significantly more patients in the desflurane group received esmolol during the prebypass period and phenylephrine during the pre- and postbypass periods to maintain hemodynamic control (table 4). Similarly, nitroglycerin was administered to treat increased pulmonary artery pressures or ECG ST-segment depression in a significantly greater number of patients in the desflurane group (n = 24) than in the sufentanil group (n = 8; $P = 0.004$) in the prebypass period. In contrast, a significantly greater number of patients in the sufentanil group received nitroprusside to reduce blood pressure during the bypass and postbypass periods.

During the prebypass period, a greater number of patients anesthetized with desflurane required nitroglycerin administration, but the incidence and severity of ECG or

TABLE 5. Hemodynamic Indices during Anesthetic Induction

	Desflurane (n = 100)	Sufentanil (n = 100)	*P*
Systolic blood pressure			
Preoperative baseline	127 ± 13	127 ± 17	
OR baseline	125 ± 22	124 ± 19	
Induction (% change)	6%	−8%	0.0001
Intubation (% change)	6%	−13%	0.0001
Diastolic blood pressure			
Preoperative baseline	75 ± 7	76 ± 7	
OR baseline	62 ± 10	62 ± 9	
Induction (% change)	19%	−7%	0.0001
Intubation (% change)	22%	−13%	0.0001
Mean arterial pressure			
OR baseline	84 ± 14	84 ± 12	
Induction (% change)	25%	−8%	0.004
Intubation (% change)	15%	−14%	0.0001
Heart rate			
Preoperative baseline	71 ± 9	70 ± 8	
OR baseline	63 ± 12	61 ± 10	
Induction (% change)	20%	−3%	0.0001
Intubation (% change)	21%	−7%	0.0001
Cardiac index			
OR baseline	2.5 ± 0.5	2.5 ± 0.5	
Induction (% change)	−10%	−9%	0.5
Intubation (% change)	−4%	−8%	0.2
Pulmonary artery systolic pressure			
OR baseline	28 ± 6	30 ± 7	
Induction (% change)	33%	7%	0.0001
Intubation (% change)	40%	6%	0.0001
Pulmonary artery mean pressure			
OR baseline	17 ± 6	18 ± 6	
Induction (% change)	68%	17%	0.0001
Intubation (% change)	83%	14%	0.0001
Pulmonary artery diastolic pressure			
OR baseline	11 ± 4	12 ± 5	
Induction (% change)	90%	17%	0.0001
Intubation (% change)	114%	15%	0.0001
Pulmonary capillary wedge pressure			
OR baseline	13 ± 4	13 ± 4	
Induction (% change)	54%	−3%	0.0001
Intubation (% change)	54%	−8%	0.0001
Central venous pressure			
OR baseline	4 ± 4	5 ± 4	
Induction (% change)	143%	63%	0.036
Intubation (% change)	190%	73%	0.013
Systemic vascular resistance			
OR baseline	1,344 ± 358	1,360 ± 334	
Induction (% change)	42%	−4%	0.03
Intubation (% change)	16%	−12%	0.0001
Pulmonary vascular resistance			
OR baseline	59 ± 8	77 ± 7	
Induction (% change)	−1%	3%	
Intubation (% change)	27%	27%	

All data are expressed as mean and ±SD as appropriate.

The *P* values indicate differences between desflurane and sufentanil groups.

TEE ischemia did not differ between anesthetic techniques. In addition, the incidence of ECG ischemia in patients who were not given nitroglycerin during maintenance of anesthesia was low (and similar) in patients who received desflurane (n = 76) and those given sufentanil (n = 92) (5% *vs.* 3%, respectively). Similarly, the incidence of prebypass TEE episodes was not significantly greater in patients who were not given nitroglycerin during maintenance of anesthesia with desflurane (n = 73) compared with those given sufentanil (n = 79) (17% *vs.* 7%, respectively; $P = 0.09$). In addition, the severity of ECG and echocardiographic ischemia was similar in patients who did not receive nitroglycerin in both anesthetic groups.

TABLE 6. Incidence and Characteristics of Holter Electrocardiographic Ischemic Episodes

	Preoperative		Induction		Pre-CPB		Post-CPB		Intensive Care Unit	
	Desflurane	Sufentanil	Desflurane	Sufentanil	Desflurane	Sufentanil	Desflurane	Sufentanil	Desflurane	Sufentanil
Hours monitored	16.0 ± 3.5	17.9 ± 7.5			1.4 ± 0.4	1.9 ± 0.8	2.0 ± 0.5	1.6 ± 0.5	43.0 ± 2.0	44.0 ± 2.0
Incidence	13%	16%	9%	0%*	7%	3%	13%	11%	4%	10%
Patients with uninterpretable Holter	4%	5%	1%	2%	1%	2%	2%	4%	2%	4%
Episodes per patient	1	1	1		1	1	1	1	1.5	1
δ ST (mm)	2.0 ± 0.6	2.3 ± 0.7	1.7 ± 0.5		1.4 ± 0.4	1.6 ± 0.8	2.4 ± 1.6	2.2 ± 0.8	3.0 ± 2.0	2.0 ± 1.0
Episode duration (min)	37 ± 32	46 ± 36	22 ± 14		17 ± 17	49 ± 19†	42 ± 34	42 ± 36	174 ± 162	195 ± 204
Duration per hours monitored	5 ± 5	6 ± 10			13 ± 11	26 ± 4	20 ± 13	27 ± 17	5 ± 5	6 ± 5
AUC per episode (mm · min)	100 ± 132	100 ± 129	18 ± 14		16 ± 13	55 ± 29‡	67 ± 72	86 ± 85	160 ± 118	253 ± 334

All data are expressed as mean ± SD.
CPB = cardiopulmonary bypass; AUC = integral of the ST-segment change over time.
* $P < 0.007$ between desflurane and sufentanil groups.
† $P < 0.04$ between desflurane and sufentanil groups.
‡ $P < 0.01$ between desflurane and sufentanil groups.

Hemodynamics

During the intraoperative period, the incidence of hemodynamic variations was low in both anesthetic groups. However, the prebypass incidence (percent of total monitoring time) of tachycardia (>120% of preoperative baseline heart rate) was higher in the desflurane group (4 ± 7%) than in the sufentanil group (1 ± 6%) ($P = 0.0003$) (fig. 1). Similarly, the incidence of prebypass hypotension (<80% of preoperative baseline SBP) was higher in the desflurane group (21 ± 14%) than in the sufentanil group (15 ± 16%) ($P = 0.01$) (fig. 2). In the postbypass period, the percent of time the hemodynamic variables were outside the specified range was similar in both anesthetic groups (fig. 3).

Myocardial Ischemia: Electrocardiography

Interpretable Holter data were obtained during the prebypass period in 197 patients, postbypass in 193 patients, and postoperatively in 194 patients (table 6). During the prebypass period (excluding the induction period), 5% (10/197) of patients developed ECG changes suggestive of ischemia, with no difference between patients who received desflurane 7% (7/99) or sufentanil 3% (3/98) ($P = 0.3$). During the postbypass period, 12% (24/194) of patients developed ECG ischemic changes, with no difference between patients who received desflurane 13% (13/97) or sufentanil 11% (11/96) ($P = 0.9$). The characteristics of ECG ischemic episodes were similar in patients in both groups except for the mean area under the curve, which was greater in the sufentanil group during the prebypass period (desflurane 16 ± 13 mm · min *vs.* sufentanil 55 ± 29 mm · min; $P = 0.01$), and episode duration, which was longer in the sufentanil group during the prebypass period (desflurane 17 ± 17 min *vs.* sufentanil 49 ± 19 min, $P = 0.04$).

Prebypass ECG ischemic episodes (excluding the induction period) were preceded by acute hemodynamic changes in 50% (4/8) of episodes in the desflurane group *versus* 0% (0/3) of episodes in the sufentanil group ($P = 0.4$). Postbypass, acute hemodynamic changes preceded ischemia in 38% (5/13) of episodes in the desflurane group *versus* 7% (1/13) of episodes in the sufentanil group ($P = 0.1$).

Myocardial Ischemia: Echocardiography

Interpretable intraoperative TEE data were obtained in 175/200 patients during the prebypass period and 178/200 patients during the postbypass period. Moderate to severe ischemic episodes (grade change ≥ 2) occurred in 12% (21/175) of patients during prebypass. The incidence of prebypass TEE episodes was not significantly greater in the desflurane group, 16% (15/91), than in

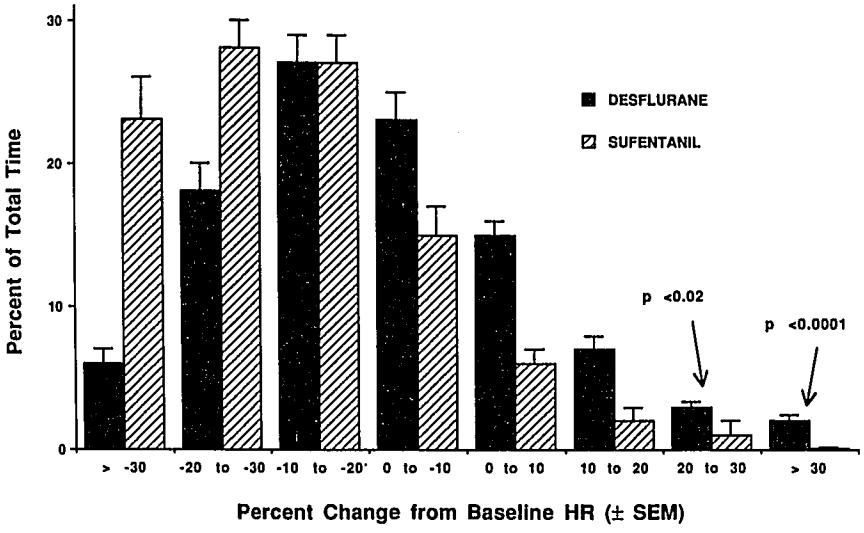

FIG. 1. The frequency distribution of heart rate (HR) as a percentage change from preoperative baseline values in 200 patients in the prebypass period.

the sufentanil group, 7% (6/84) ($P = 0.09$). TEE ischemic episodes occurred in 27% (49/178) of patients during the postbypass period, with no difference between the desflurane (29%, 27/92) and sufentanil (25%, 22/86) groups ($P = 0.7$). The characteristics of prebypass and postbypass TEE ischemic episodes were similar in the two groups (table 7). Prebypass, acute hemodynamic changes preceded TEE ischemic episodes in 52% (10/19) of episodes in the desflurane group and 43% (3/7) of episodes in the sufentanil group ($P = 1$); postbypass, acute hemodynamic changes preceded 32% (11/34) of episodes in the desflurane group and 50% (13/26) of episodes in the sufentanil group ($P = 0.3$).

Medications (*i.e.*, sedatives/analgesics, vasodilators, vasopressors, and antiarrhythmics) used on the day of surgery and postoperative days 1 and 2 were similar in both groups.

Myocardial Ischemic Effects: Steal-prone Anatomy

We examined the incidence of myocardial ischemia in patients with or without steal-prone coronary artery anatomy in the desflurane group. Myocardial ischemia (ECG or echocardiography [precordial or TEE]) occurred in 28% (25/90) of patients during the prebypass period, with no increased incidence in the steal-prone group (12%, 3/24) compared to the non–steal-prone group (33%, 22/66) ($P = 0.05$).

OUTCOME MEASUREMENTS

Adverse cardiac outcomes of cardiac death, myocardial infarction, or ventricular failure occurred in 6.5% (13/200) patients, with no significant difference between groups (table 8).

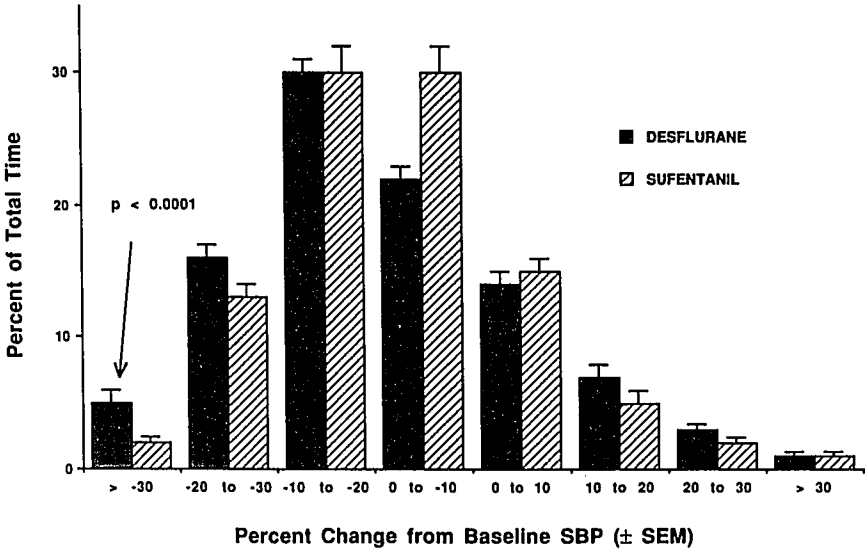

FIG. 2. The frequency distribution of systolic blood pressure (SBP) as a percentage change from preoperative baseline values in 200 patients in the prebypass period.

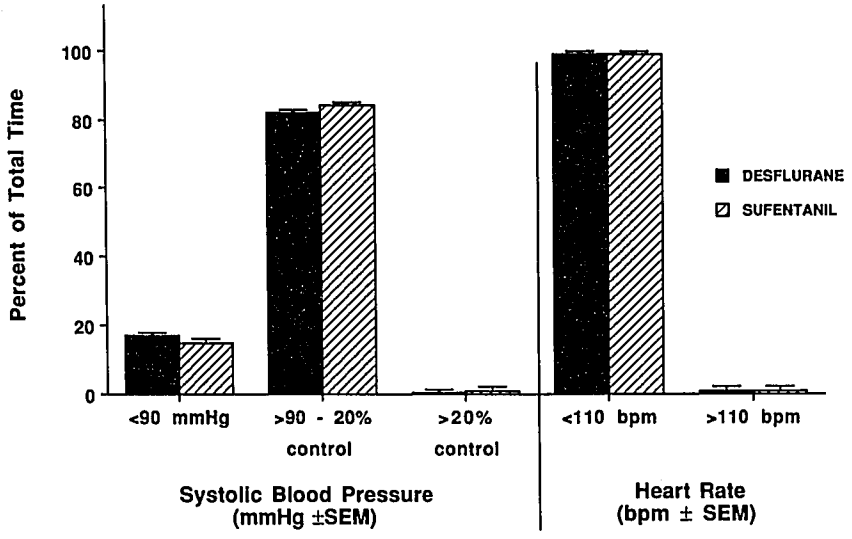

FIG. 3. The frequency distribution of heart rate (HR) < 100 beats per min (bpm) and >100 beats per min in the postbypass period; the frequency distribution of systolic blood pressure (SBP) < 90 mmHg, between 90 mmHg and 120% of preoperative baseline values, and >120% preoperative baseline values in 200 patients in the postbypass period.

Discussion

Our study demonstrates that induction of anesthesia with desflurane is associated with greater hemodynamic instability and myocardial ischemia than is induction with sufentanil, despite aggressive attempts at rigorous hemodynamic control. However, maintenance of anesthesia with desflurane or sufentanil as the primary agent results in a similar risk of myocardial ischemia, when hemodynamics are well controlled.

INDUCTION OF ANESTHESIA

Hemodynamics

In both swine and canine models,[20–23] heart rate increases, systemic blood pressure decreases, myocardial contractility decreases, coronary blood flow increases, coronary vascular resistance decreases, and pulmonary artery pressures remain unchanged during increasing concentrations of desflurane anesthesia.

There are few conclusive studies in humans documenting desflurane's cardiovascular effects during induction of anesthesia. The initial trials in young, healthy, male volunteers given concentrations of desflurane of up to 6% produced decreases in systemic blood pressure and minimal changes in heart rate from control values.[24] Desflurane also caused a dose-dependent increase in right-heart filling pressure and a decrease in systemic vascular resistance, but in another study[25] caused an increase in heart rate. In our patients undergoing CABG surgery, induction of anesthesia (at ≈ 1.0–2.0 MAC) with thio-

TABLE 7. Incidence and Characteristics of Transesophageal Echocardiographic Ischemic Episodes

	Pre-CPB		Post-CPB	
	Desflurane	Sufentanil	Desflurane	Sufentanil
Hours monitored	1.2 ± 1.1	1.2 ± 0.5	1.1 ± 0.8	1.0 ± 0.4
Incidence	16%	7%	29%	25%
Patients with uninterpretable TEE	9%	16%	8%	14%
Episodes per patient	1	1	1	1
Episode duration (min)	17 ± 12	14 ± 11	19 ± 18	30 ± 31
Ischemic minutes per hours monitored	19 ± 19	14 ± 11	23 ± 21	33 ± 20
Location of SWMA per patient				
Posterior	40%	67%	74%	82%
Septum	53%	33%	37%	36%
Anterior	20%	33%	29%	32%
Lateral	20%	17%	18%	9%
Number of walls				
1	80%	68%	59%	54%
2	13%	16%	33%	32%
3	7%	16%	4%	14%
4			4%	0%

All data are expressed as mean and ±SD as appropriate.

TEE = transesophageal echocardiography; SWMA = segmental wall motion abnormalities.

TABLE 8. Incidence of Adverse Cardiac Outcomes

	Desflurane	(n = 100)	Sufentanil	(n = 100)
Cardiac injury				
CPK-MB				
Patients with >50 U/l	33	33%	34	34%
Mean (±SD) CPK-MB (all patients)	57 ± 69		52 ± 46	
Median CPK-MB (all patients)	33		35	
Adverse cardiac outcomes				
Ventricular failure	1	1%	1	1%
Myocardial infarction	4	4%	4	4%
Death				
Cardiac	1	1%	2	2%
Noncardiac	0	0%	1	1%
Total cardiac outcomes (ventricular failure, myocardial infarction, and cardiac death)	6	6%	7	7%

Ventricular failure: cardiac index < 2 $l \cdot min^{-1} \cdot m^{-2}$ and requirement for an intraaortic balloon pump.

CPK-MB = MB isoenzyme of creatine phosphokinase (U/l).

pental followed by desflurane produced substantial increases in systemic arterial (6–25% of baseline), pulmonary arterial (33–100% of baseline), and pulmonary capillary wedge pressures (50% of baseline). However, cardiac index remained unchanged because although stroke volume decreased significantly, there was a 20% increase in heart rate at induction and intubation. In addition, the difficulty of administering desflurane alone was demonstrated by the marked hemodynamic changes that occurred during induction despite aggressive attempts to maintain hemodynamic control. In contrast, patients who received sufentanil manifested significantly less hemodynamic change during induction.

Therefore, our hemodynamic results are similar to those reported by Weiskopf *et al.*[25] except for increases in systemic arterial pressure in our patients. Potential etiologies for desflurane's hemodynamic effects in our patients include peripheral stimulation with an increase in afterload (*e.g.*, increased circulating catecholamines[26]), depression of myocardial contractility (as has been suggested in canine studies[23] and studies of healthy volunteers[25]), or myocardial ischemia. Other etiologies, such as inadequate anesthetic depth, excitement, airway obstruction, hypercarbia, or hypoxia, did not occur during the course of induction or intubation.

Ross *et al.*[27] also studied patients undergoing CABG surgery (n = 22), comparing the hemodynamic effects of induction of anesthesia with desflurane or isoflurane combined with sodium thiopental (2 mg/kg) and fentanyl (5 μg/kg). Although they also observed a significant increase in pulmonary arterial mean and pulmonary capillary wedge pressures during induction of anesthesia with desflurane, the magnitude of the change was much less than that observed in our patients, and systemic arterial pressures were unchanged. Similarly, Thomson *et al.*[28] compared desflurane with isoflurane using similar adjuvants (thiopental and fentanyl [10 μg/kg]) as Ross *et al.*, and found no significant hemodynamic changes during induction or intubation in the same surgical population. Our technique of induction (desflurane with thiopental adjuvant only) is more similar to that reported by Weiskopf *et al.*,[25] who used an inhalational induction of desflurane without opioid adjuvants. If the cardiovascular response to desflurane (increases in heart rate and blood pressure) is mediated by the sympathetic nervous system, then the use of fentanyl in the studies by Thomson *et al.*[28] and Ross *et al.*[27] may have blunted the magnitude of hemodynamic changes during induction of anesthesia with desflurane.

Myocardial Ischemic Effects

There have been no animal studies examining the effects of induction of anesthesia with desflurane on myocardial ischemia. In humans, myocardial ischemia during anesthetic induction has been demonstrated with all anesthetics using ECG and radionuclear and biochemical markers, but the reported incidence and severity of ischemia vary widely due to study design and methodologic differences. Studies of induction of anesthesia with volatile agents (with and without sodium thiopental or etomidate) have been shown to produce ischemia in patients undergoing CABG surgery.[8–14] However, the findings of studies that have examined the induction of anesthesia using pure inhalational techniques have been limited by the study size and the differences in the myocardial ischemia detection techniques (biochemical *vs.* ECG *vs.* radionuclear, intermittent *vs.* continuous), as well as hemodynamic control.

Slogoff and Keats[15] reported a relatively high incidence of ischemia during the induction of anesthesia using a volatile agent/opioid technique or opioid only, compared with induction with volatile agents alone. Using intermittent ECG detection, Slogoff and Keats[15] induced anesthesia in 1,012 CABG patients using fentanyl (5 μg/kg)

and halothane, enflurane, or isoflurane, or sufentanil alone (20–30 μg/kg) and found that there was no difference in the incidence of ischemia with all three volatile anesthetic/opioid techniques (halothane, 19%; enflurane, 18%; isoflurane, 16%) and slightly higher with sufentanil alone (25%). However, this study was limited by the use of an intermittent method for the detection of ischemia and substantial hemodynamic variations. In contrast, Leung *et al.*[16] used continuous two-lead Holter ECG during induction of anesthesia in 111 CABG patients given sufentanil alone (5–10 μg/kg) and 54 patients given isoflurane (with fentanyl, 5–10 μg/kg) and found a much lower incidence of myocardial ischemia, *i.e.*, 3.6%, 1.9%, respectively. These results suggest that the reported incidence of ischemia differs because of the sensitivity of the detection technique and (perhaps more importantly) the degree of hemodynamic control. The hemodynamic control (SBP and heart rate ± 20% of baseline values) imposed in the study by Leung *et al.*[16] may have reduced the incidence of ischemia despite their use of a more sensitive technique for detection of ischemia.

We examined desflurane as a sole anesthetic induction agent to determine its potential safety for use in patients with coronary artery disease. We chose patients undergoing CABG surgery as a model because they have well-defined coronary anatomy. In addition, we wanted to avoid the limitations of the previous studies, which include study size, ischemia detection methodology (sensitivity), and sampling intervals (intermittent *vs.* continuous) and the use of opioid adjuvants. Using simultaneous sensitive and continuous measures of ischemia—Holter ECG and precordial echocardiography—while aggressively attempting to maintain hemodynamic control, we found no ECG or echocardiographic evidence of ischemia during induction of anesthesia with sufentanil but a 9% incidence of ECG ischemia and 13% incidence of echocardiographic ischemia during induction with desflurane. Our findings suggest that the use of desflurane as a sole agent (with thiopental) for induction of anesthesia increases the risk of myocardial ischemia in patients with coronary artery disease; therefore, its use as a single agent for induction in such a high-risk population may be undesirable. Although desflurane would not likely be used as a *sole* agent in cardiac surgery, it is likely to be used as a sole agent in noncardiac surgery if clinicians were to attempt to capitalize on its characteristics of rapid emergence and recovery, especially in ambulatory surgical settings. Therefore, examining the cardiovascular effects of desflurane as a sole agent in patients with coronary artery disease is warranted.

Our use of desflurane as the primary anesthetic for induction of anesthesia enhanced our ability to uncover the cardiovascular effects of desflurane in our population, without the confounding effects of adjunctive opioid administration. For example, Thomson *et al.*[28] detected no acute myocardial ischemia (continuous ECG monitoring) in the same surgical population during induction of anesthesia with desflurane and fentanyl, suggesting that fentanyl administration may have had a suppressive effect on the risk of ischemia. The low incidence of myocardial ischemia during induction of anesthesia with sufentanil in our patients indicates that, perhaps, the choice of anesthetic may be important during this period.

Maintenance of Anesthesia

Hemodynamics

The effects of maintenance of anesthesia with desflurane on myocardial perfusion have been studied in a chronic ischemia canine model.[29] Investigators observed that maintenance of anesthesia with desflurane does not redistribute myocardial blood flow from collateral-dependent poststenotic regions, especially with stable hemodynamic variables.

During maintenance of anesthesia in healthy volunteers, light levels (4.8–6.0%) of desflurane neither depress nor stimulate heart rate or blood pressure significantly.[24] At these doses, desflurane does not prevent acute increases in heart rate during excitement or tetanic, supramaximal electrical stimulation of the ulnar nerve. At deeper levels of anesthesia (>1.5 MAC), heart rate increases in healthy volunteers.[30]

In our patients undergoing CABG surgery, we found that maintenance of anesthesia with desflurane resulted in a greater incidence of hypotension and tachycardia during the prebypass period than did sufentanil anesthesia, although the incidence of tachycardia was low in both groups. Thomson *et al.*[28] found that hemodynamic change (measured intermittently) during the prebypass period was similar during desflurane as compared to isoflurane anesthesia with fentanyl used as an adjuvant. A 15% increase in heart rate and 10% decrease in MAP occurred at sternotomy in both groups. The findings from these two studies suggest that supplementing desflurane anesthesia with an opioid agent for maintenance of anesthesia may be desirable in this patient population. However, such a supposition must be examined scientifically. We chose to use desflurane alone (with the exception of thiopental) to evaluate its effects on hemodynamic indices in high-risk patients. One consequence of our use of desflurane alone was a greater incidence of therapeutic intervention to maintain hemodynamic control (reflected in the significantly greater use of phenylephrine during the pre- and postbypass periods and esmolol during the prebypass periods) than in our sufentanil group. The incidence of hemodynamic deviation from baseline values during desflurane anesthesia might have been greater had pharmacologic interventions (*i.e.*, nitrates, β-blocking agents) not been implemented. In addition, the incidence

of hemodynamic variability (and perhaps myocardial ischemia) may have been attenuated during the postbypass period secondary to the presence of residual sufentanil administered during the bypass period.

Myocardial Ischemic Effects

A previous study in dogs suggested that maintenance of anesthesia with desflurane does not precipitate myocardial dysfunction (decreased segmental shortening).[29] In our patients, the incidence of ischemia associated with maintenance of anesthesia with desflurane did not differ from that associated with sufentanil anesthesia, using either ECG or echocardiographic measures.

The incidence of ECG ischemia in our patients during both the prebypass and postbypass periods did not differ by anesthetic technique, but the severity of ischemia was significantly greater during the prebypass period with sufentanil anesthesia. The ischemic episode duration *per se* was shorter and the area under curve was smaller in the desflurane group. The difference in the latter two variables may have been secondary to the higher incidence of pharmacologic intervention (*i.e.*, nitrates, β-blocking agents) required during desflurane anesthesia during the prebypass period to control the hemodynamics. Although Thomson *et al.*[28] reported a much greater (14%) incidence of ECG ischemia during the prebypass period with desflurane anesthesia, interpretation of this finding is limited by several confounding factors, including sample size (n = 21) and use of an opioid adjuvant.

The greater association of hemodynamic variability preceding both ECG (33%) and TEE (50%) ischemia in the desflurane group as compared to the sufentanil group despite continuous and invasive hemodynamic monitoring (systemic arterial and pulmonary artery catheters) and more frequent pharmacologic therapy indicate that it is difficult to administer desflurane as a sole maintenance anesthetic.

Clinical Implications

Our findings demonstrate that the risk of myocardial ischemia and of hemodynamic instability in patients with known coronary artery disease is greater during induction of anesthesia with desflurane as the primary anesthetic (*i.e.*, without adjuvants except for thiopental) than with sufentanil. In addition, hemodynamic stability is difficult to achieve during induction with desflurane, despite continuous hemodynamic monitoring and frequent pharmacologic intervention.

Desflurane appears to be safe to use as the primary maintenance anesthetic in high-risk patients when hemodynamics are controlled. The risk of ischemia in our patients undergoing CABG surgery was no different from that associated with sufentanil anesthesia, nor was the incidence of adverse cardiac outcome different (although our number of outcomes was small).

Our study did not address at-risk patients undergoing noncardiac procedures, which is a much larger population, and study of safety and efficacy is warranted in this population before widespread use.

Limitations

Several potential limitations exist in this study. First, because there is no absolute reference for measuring myocardial ischemia, validation of either precordial and TEE indices of ischemia (regional wall-motion changes) or ECG indices (ST-segment changes) is difficult. However, regional wall-motion changes have been shown to be sensitive and early markers of myocardial ischemia by a number of experimental and clinical studies in animals and humans.[3,7,31–38] Similarly, although there are nonischemic etiologies for ST-segment changes, including body temperature, serum electrolytes, ventilatory or positional changes, or use of vasoactive drugs, the strong relationship between ST-segment abnormalities and the subsequent development of adverse cardiac outcomes suggests the predictive validity of ST-segment abnormalities.[1] An additional limitation of the precordial echocardiographic technique was the difficulty in obtaining an optimal view of the left ventricle while the patient was in the supine position for anesthetic induction, resulting in a relatively small number (68/120) of analyzable images. Nonetheless, these were sufficient to determine a substantial difference in the incidence of ischemia between anesthetic techniques.

Second, desflurane could not be administered during cardiopulmonary bypass in our patients because the necessary technology (vaporizer) was not available.‡‡ Therefore, we administered sufentanil to maintain anesthesia in both groups, thereby potentially confounding our anesthesia-related comparison of postbypass ischemia and associated outcomes.

Third, the intraoperative use of nitroglycerin to treat elevated pulmonary artery pressures and/or detected changes in ST-segment or T-wave morphology may have confounded our detection of the incidence and magnitude of ischemic episodes. However, the use of nitroglycerin during induction of anesthesia was infrequent (and similar) in patients who received desflurane and those given sufentanil. During the prebypass period, a greater number of patients anesthetized with desflurane required nitroglycerin administration, but the incidence and severity of ECG or TEE ischemia did not differ between anesthetic techniques.

Fourth, more rigorous control of hemodynamics may have reduced the incidence of myocardial ischemia during

‡‡ Anaquest: Personal communication. August, 1991.

both induction and maintenance of anesthesia in the desflurane group. The use of opioids may have improved our hemodynamic control, but this would have interfered with the study's goals.

Fifth, our sample size was insufficient to detect a significant difference in adverse cardiac outcome between groups. However, because the incidence of outcome was low and nearly identical, no significant difference would have been detected even if the sample size was increased by 10-fold. In addition, although the incidence of moderate to severe ischemic prebypass TEE ischemic episodes was not significantly greater in the desflurane group (16%) than in the sufentanil group (7%) ($P = 0.09$), the relative risk was 2.3 (95% confidence interval 0.9–5.7). Thus, we cannot exclude the possibility of a small difference in ischemia between the two anesthetics during the prebypass period.

Finally, there may have been an association between the clinicians' experience with the use of desflurane that contributed to the development of hemodynamic aberration and thus potentially to the development of ischemia. However, we examined the relationship of the magnitude of hemodynamic change to clinical experience with desflurane and found no evidence of more hemodynamic changes or myocardial ischemia in the early part of the study. Desflurane was administered by four anesthesiologists, each with greater than 10 yr of experience, whose practice is exclusively cardiac anesthesia.

Applying continuous ECG and echocardiographic measures of ischemia, we found that the risk of myocardial ischemia was not significantly increased during maintenance of anesthesia with desflurane as a primary anesthetic relative to sufentanil anesthesia, when hemodynamics were controlled. Desflurane therefore appears to be safe to maintain anesthesia in the cardiac surgical population. In contrast, desflurane anesthesia incurred a 9–13% incidence of myocardial ischemia during induction of anesthesia, while sufentanil incurred none. In addition, the magnitude of hemodynamic change was significantly greater during induction with desflurane ($\approx$ 1.0–2.0 MAC) than during induction with sufentanil despite aggressive attempts to maintain control of hemodynamics. Concomitant administration of opioid or other adjuvant agents may mitigate the deleterious effects of desflurane during induction, but this remains to be proven.

Extrapolation of these findings to the at-risk patient undergoing noncardiac surgery is not warranted. However, we caution against the use of desflurane as the primary agent during induction in this population because it may produce adverse hemodynamic and ischemic effects similar to those we have observed in our cardiac surgical patients. To address these issues, it is necessary to perform further studies of the induction and maintenance effects of desflurane in the at-risk patient undergoing noncardiac surgery.

The authors thank Hewlett-Packard for providing equipment and Winifred von Ehrenburg for editorial assistance.

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Appendix

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