

Myocardial Circulatory and Metabolic Effects of Isoflurane and Sufentanil during Coronary Artery Surgery

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The global and regional coronary hemodynamic and myocardial metabolic effects of isoflurane administered intraoperatively as an adjunct to sufentanil were studied in seven of nine patients who experienced increased systemic arterial pressure while undergoing elective coronary artery bypass grafting. All patients were premedicated and maintained on their preoperative medications (β -blockers, nitrates, Ca^{++} entry blockers) up to and including the morning of surgery. Systemic and pulmonary hemodynamics and global (coronary sinus, CS) and regional (great cardiac vein, GCV) coronary blood flows were measured, and blood samples were obtained for systemic and myocardial metabolic parameters: a) after induction with 30 mcg/kg of sufentanil and 0.12 mg/kg vecuronium ($F_{I_{O_2}}$ 1.0), but prior to incision (control); b) 5 min after sternotomy; and c) during ventilation with isoflurane-oxygen. Heart rate, cardiac output, stroke volume, and GCV/CS flow ratio did not change throughout the study. Neither global nor regional myocardial lactate production was detected in any patient at any time, and the electrocardiogram (lead II, V5) remained unchanged. In response to sternotomy, seven of nine patients experienced an increase in mean systemic arterial pressure of 20% or more ($27 \pm 3\%$ from control values), due to an elevation in systemic vascular resistance ($30 \pm 5\%$). Coronary sinus (CS) and great cardiac vein (GCV) flows, as well as CS and GCV lactate extractions, were unchanged 5 min after sternotomy. Both global and regional myocardial oxygen extraction increased, while coronary venous oxygen content decreased. Isoflurane was administered in a dose that restored systemic arterial pressure to baseline values (inspired concentration 0.75–1.0%). Concomitantly, global and regional myocardial oxygen extraction and venous oxygen content returned toward control values. These data suggest that, in doses which produce no significant hypotension, isoflurane is a safe and effective adjunct for control of intraoperative elevation of systemic arterial pressure and vascular resistance during high dose sufentanil anesthesia in patients undergoing elective coronary artery bypass grafting. (Key words: Anesthesia: cardiac. Anesthetics, intravenous: sufentanil. Anesthetics, volatile: isoflurane. Heart: coronary artery disease; coronary circulation; coronary occlusion; ischemia; metabolism; myocardial.)

MANY PATIENTS with coronary artery disease who are anesthetized with a high dose of narcotics experience sys-

temic hypertension and vasoconstriction, and tachycardia in response to sternotomy.¹⁻³ It is common practice to supplement narcotic anesthesia with inhalational anesthetics to relieve these adverse hemodynamic events.

A recent report demonstrated that isoflurane (1.5–2% inspired concentration) is an effective treatment for intraoperative hypertension in patients with severe ischemic heart disease.⁴ No electrocardiographic evidence of myocardial ischemia was observed, while left ventricular performance improved (increased stroke volume, decreased pulmonary capillary wedge pressure). In a subsequent study, Tarnow *et al.*⁵ reported that isoflurane at low concentrations (0.5% end-tidal) improved the tolerance to pacing-induced myocardial ischemia in patients with significant coronary artery disease. No ECG changes of ischemia were evident during isoflurane. Myocardial hemodynamics and metabolic evaluation were not performed in these two studies.^{4,5} Others have reported a high incidence of myocardial ischemia with isoflurane, as evidenced by ECG changes and/or myocardial metabolic abnormalities.⁶⁻⁸ These studies, which were performed during induction of anesthesia and prior to surgical stimulation, used isoflurane or isoflurane-N₂O as the principal anesthetic.

The global and regional myocardial circulatory and metabolic effects of isoflurane as a supplement to a high dose of narcotics have not been evaluated. The present study was performed to define: a) the effects of isoflurane as an adjunct to a high dose of sufentanil on systemic and pulmonary hemodynamics, and on global and regional myocardial circulation and metabolism in patients with severe ischemic heart disease; and b) its effectiveness in controlling post-sternotomy increases in systemic arterial pressure and vascular resistance.

Materials and Methods

PATIENTS

Nine patients scheduled for elective coronary artery bypass grafting were entered into the study after informed consent was obtained. Demographic data for all patients is shown in table 1. All patients were maintained on their preoperative cardiac medications, and received them the

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TABLE 1. Demographic Data

Patient #	Age	Sex	EF	# Grafts	WM	Medications		
						N	B	C
1	68	M	55	2	+	+	-	+
2	64	M	50	6	+	+	-	+
3*	60	M	72	5	+	+	+	+
4	57	F	60	1	+	+	+	+
5*	60	M	54	3	-	+	+	+
6	59	M	64	5	+	+	+	+
7	66	M	43	2	+	+	+	+
8	55	M	71	4	+	+	+	+
9	53	M	60	2	+	+	+	+

EF = ejection fraction; WM = wall motion abnormalities; N = nitrates; B = beta blockers; C = calcium channel blockers;

+ = present; - = absent.

* No isoflurane.

morning of surgery. We excluded patients with an ejection fraction less than 40% as determined by cineangiography, associated significant valvular disease, or a history of congestive heart failure. In response to sternotomy, seven of these patients experienced an increase in mean systemic arterial pressure greater than 20% from pre-incision (control) values, and comprised the study group.

STUDY PROTOCOL AND MEASUREMENTS

Premedication consisted of intramuscular morphine sulfate (0.1 mg/kg), scopolamine (0.4 mg), and oral lorazepam (1-2 mg). An additional 1-2 mg of lorazepam was given intravenously during catheter placement.

A Baim coronary sinus catheter⁹ (Elecath Corp., Rahway, New Jersey) and a triple lumen pacing pulmonary artery catheter were inserted using the Seldinger technique *via* the right internal jugular vein under fluoroscopic guidance to ensure proper placement. The Baim catheter was positioned 2 cm beyond the coronary sinus (CS) into the great cardiac vein (GCV). This catheter has two sampling ports available, through which blood may be sampled from the coronary sinus and great cardiac vein. Two thermistors at 5 mm and 35 mm from the tip of the catheter are used for coronary sinus (CS) and great cardiac vein (GCV) flow determination.

Appropriate positioning of the CS catheter was confirmed by injection of 2-3 ml contrast medium, radiologic visualization, and by continuous pressure monitoring.

Hemodynamic measurements which included systemic arterial (SAP), pulmonary arterial (PAP), pulmonary capillary wedge (PCWP), and right atrial (RAP) pressures (mmHg), and heart rate (HR) were recorded throughout the study on a strip chart recorder. All transducers were zeroed at the level of the mid-chest and calibrated against a mercury manometer. After each set of measurements, all pressure channels of the chart recorder were checked

for zero-drift. ECG leads II and V5 were monitored continuously on an oscilloscope and recorded intermittently at 25 mm/sec. Cardiac output (CO, l/min), coronary sinus blood flow (CSF, ml/min), and great cardiac vein flow (GCVF, ml/min) were measured in duplicate by thermodilution.¹⁰ To perform the measurements of myocardial blood flows, the infusion rate of the indicator was 46 ml/min. The infusate was normal saline at room temperature.

Blood samples for lactate assay (mmol/l) (perchloric acid method, Boehringer Mannheim) and O₂ content measurements (ml/dl) (galvanic cell method, LexO₂con, Lexington Instruments) were withdrawn simultaneously from the CS, GCV, mixed venous, and arterial sites. Under the conditions of the lactate assay, all measured change of absorbance relates to L-lactate. The sensitivity of the assay is limited by a difference of 0.020 absorbance unit, which corresponds to 1 mg lactic acid/dl blood (340 nmol).¹¹ A comparison of the Boehringer Mannheim method with the assay method described by Gutmann and Wahlefeld resulted in a linear regression slope of $y = 0.05 + 0.991x$, and a correlation coefficient of 0.96 was found.¹¹

Stroke volume (SV, ml), systemic (SVR) and pulmonary (PVR) vascular resistances ($\text{dyn} \cdot \text{sec} \cdot \text{cm}^{-5}$), global and regional myocardial oxygen consumption (global-M $\dot{V}O_2$, regional-M $\dot{V}O_2$, ml/min), and lactate extraction (global-MLE, regional-MLE, %) were calculated by standard formulae.

PROTOCOL

Anesthesia was induced with a 30 mcg/kg sufentanil infusion lasting 20 min; vecuronium was administered (0.12 mg/kg) to facilitate intubation. Ventilation was controlled (FI_{O₂} 1.0) using a semi-closed system with partial rebreathing and high fresh gas inflow (8 L/min). An

isoflurane vaporizer (ISOTEC® 4, OHMEDA, Madison, WI) was used, and its calibration was checked against Reiken refractometer.

In all patients (n = 9) hemodynamic measurements were performed and blood samples obtained after induction of anesthesia, prior to surgical stimulation (pre-incision, control) and 5 min after sternotomy. An additional set of measurements was taken in seven patients during isoflurane-oxygen inhalation. Isoflurane was administered when an increase of the mean SAP of greater than 20% from pre-incision values was observed after sternotomy. Before data were collected, isoflurane was administered for at least 10 min (13 ± 2 min), and the inspiratory concentration was titrated (vaporizer dial setting 0.75–1%) to restore mean SAP toward control values. End-tidal concentration of isoflurane was not measured. P_{aCO_2} was monitored continuously by infrared capnometry, and ventilation was adjusted to maintain end tidal P_{CO_2} in the physiologic range. In five of the seven patients, isoflurane oxygen was continued throughout the pre-cardiopulmonary bypass period, and adjusted to maintain the arterial pressure at control values. In the remaining patients, isoflurane was discontinued to prevent further decrease in arterial pressure.

Criteria of myocardial ischemia used in this study included an increase in PCWP to >15 mmHg with or without prominent waves, ST-segment changes of >0.1 mV, T-wave inversions, and/or myocardial lactate production.

The surgical procedure was not interrupted during the study, since we were evaluating the effects of sufentanil and isoflurane under clinical conditions. However, manipulation of the heart was avoided during the study and collection of data. There were no complications from pulmonary artery or coronary sinus catheterization.

No control group was evaluated, since our study was designed specifically to investigate whether isoflurane inhalation under specific circumstances would be associated with myocardial ischemia.

Data were analyzed with repeated measures analysis of variance (BMDP statistical software). When P values were less than 0.05, the Student-Newman-Keuls multiple range test was used to assess intragroup differences. All results are reported as mean \pm standard error, unless otherwise stated.

Results

Systemic pulmonary and coronary hemodynamic data, as well as myocardial metabolic data, are presented in tables 2 and 3. Heart rate, cardiac index, and stroke volume index did not change during the study. Hematocrit was also unaltered.

TABLE 2. Systemic and Pulmonary Hemodynamic Changes in Response to Sternotomy and During Isoflurane Administration (Mean \pm SE)

	Pre-incision	Sternotomy	Isoflurane
HR bpm	47.0 \pm 3.1	53.1 \pm 3.7	48.0 \pm 3.2
MSAP mmHg	71.0 \pm 3.1	90.4 \pm 3.8*	69.6 \pm 4.3§
MPAP mmHg	15.5 \pm 1.5	19.1 \pm 1.2*	14.3 \pm 1.2§
PCWP mmHg	10.9 \pm 1.4	14.0 \pm 1.4†	9.9 \pm 1.1§
RAP mmHg	5.6 \pm 1.1	7.1 \pm 1.1‡	4.6 \pm 0.8¶
CI l/min	2.44 \pm 0.2	2.60 \pm 0.2	2.33 \pm 0.4
SVI ml	52.8 \pm 3.5	50.4 \pm 4.8	49.3 \pm 3.4
SVR dyn \cdot sec \cdot cm ⁻⁵	1073 \pm 67	1590 \pm 63‡	1147 \pm 85**
PVR dyn \cdot sec \cdot cm ⁻⁵	75.7 \pm 12.7	69.6 \pm 11.8	79.0 \pm 6.1

MSAP = mean systemic arterial pressure; MPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; CI = cardiac index; SVI = stroke volume index; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance.

From pre-incision: * $P < 0.01$; † $P < 0.02$; ‡ $P < 0.05$.

From sternotomy: § $P < 0.01$; ¶ $P < 0.02$; ** $P < 0.05$.

EFFECT OF STERNOTOMY

Sternotomy was associated with an increase in mean systemic arterial pressure (27%, $P < 0.01$), due to an increase in systemic vascular resistance (30%, $P < 0.01$) (table 2). In addition, mean pulmonary arterial, pulmonary capillary wedge, and right atrial pressures increased significantly. PVR did not change. In response to sternotomy, both regional and global myocardial oxygen consumption increased significantly as reflected by decreased oxygen content in the GCV and CS respectively (table 3). Coronary sinus and great cardiac vein flow did not change significantly, and their ratio was unaltered. No global or regional myocardial lactate production was observed in any patient (table 3). One patient, however, developed large a- and v-waves in PCWP tracing suggestive of decreased ventricular compliance. In another patient, ST-segment and T-wave abnormalities suggestive of myocardial ischemia were detected during sternotomy. No ECG abnormalities were observed in the remainder of the patients.

EFFECT OF ISOFLURANE ADMINISTRATION

Isoflurane restored mean systemic arterial pressure to pre-incision levels without significantly altering heart rate, stroke index, or cardiac index (table 2). Systemic vascular resistance, and mean pulmonary arterial right atrial and pulmonary capillary wedge pressures, all decreased significantly toward control values (Table 2). Concomitantly, coronary sinus and great cardiac vein oxygen extraction decreased significantly (approximately 15%, $P < 0.001$), from post-sternotomy values (table 3). Global and regional coronary blood flow did not change significantly, although

TABLE 3. Coronary Hemodynamic and Myocardial Metabolic Changes in Response to Sternotomy and during Isoflurane Administration (Mean \pm SE)

	Pre-Incision	Sternotomy	Isoflurane
Coronary Sinus (Global)			
CSF (ml/min)	117.5 \pm 11.3	123.8 \pm 10.8	115.1 \pm 12.9
CS O ₂ Content (ml/dl)	6.71 \pm 0.19	5.60 \pm 0.25*	7.09 \pm 0.24§
Global O ₂ Ext (%)	63.55 \pm 1.26	69.80 \pm 1.17†	61.38 \pm 1.29§
Global M \dot{V} O ₂ (ml/min)	13.61 \pm 1.11	15.87 \pm 1.17*	12.90 \pm 1.39¶
CS Lactate (mmol/l)	0.805 \pm 0.14	0.782 \pm 0.09	0.792 \pm 0.08
Global Lac Ext (%)	47.31 \pm 5.79	48.42 \pm 4.03	37.09 \pm 3.67‡**
Great Cardiac Vein (Regional)			
GCV Blood Flow (ml/min)	81.0 \pm 9.8	78.5 \pm 8.9	69.0 \pm 10.5
GCV O ₂ Content (ml/dl)	6.44 \pm 0.33	5.24 \pm 0.17‡	6.83 \pm 0.25§
Regional O ₂ Ext (%)	65.14 \pm 1.54	71.65 \pm 1.11‡	62.79 \pm 1.29§
Regional M \dot{V} O ₂ (ml/min)	9.59 \pm 0.92	10.84 \pm 1.01‡	7.86 \pm 1.02**
GCV Lactate (mmol/l)	0.729 \pm 0.11	0.686 \pm 0.07	0.713 \pm 0.08
Regional Lac Ext (%)	51.34 \pm 4.39	53.55 \pm 5.20	43.54 \pm 3.04‡**

CSF = coronary sinus blood flow; CS O₂ content = coronary sinus oxygen content; Global O₂ Ext = global myocardial oxygen consumption; Global M \dot{V} O₂ = global myocardial oxygen consumption; Global Lac Ext = global lactate extraction; GCV = great cardiac vein; GCV O₂ Content = regional oxygen content; Regional O₂ Ext = Regional vein myocardial oxygen extraction; Regional M \dot{V} O₂ = regional vein myocardial oxygen consumption; Regional Lac Ext = regional lactate extraction.

From pre-incision: * $P < 0.01$; † $P < 0.01$; ‡ $P < 0.05$.

From sternotomy: § $P < 0.01$; ¶ $P < 0.01$; ** $P < 0.05$.

myocardial oxygen consumption, oxygen content difference, and myocardial lactate extraction all declined (table 3). As before, no global or regional lactate production was detected in any patient. The electrocardiographic changes observed in one patient during sternotomy, and the prominent a- and v-waves noted in another patient, gradually resolved.

Discussion

The effect of isoflurane on myocardial blood flow and metabolism remains controversial. Some investigators have observed a dose-related reduction in canine myocardial blood flow and oxygen consumption (M \dot{V} O₂),^{12,13} while coronary arteriovenous oxygen difference and cor-

onary vascular resistance were unaltered.¹² In contrast, others have reported an increase in canine myocardial blood flow with isoflurane, despite a decrease in myocardial oxygen requirements.¹⁴ It has been suggested that isoflurane is a coronary vasodilator, which may alter the pressure-flow relationship (coronary autoregulation).^{14,15}

Clinical data demonstrate electrocardiographic and/or metabolic evidence (lactate production) of myocardial oxygen imbalance during isoflurane or isoflurane-nitrous oxide anesthesia in patients with severe ischemic heart disease.^{6-8,16,17} Reiz *et al.*⁶ demonstrated ECG and metabolic evidence of myocardial oxygen imbalance in non-premedicated patients during prolonged exposure to isoflurane (1% end-tidal) in the absence of surgical stimulation. Decreased myocardial lactate extraction and elevated coronary venous oxygenation was associated with marked systemic hypotension and fall in stroke volume. Despite restoration of perfusion pressure with phenylephrine, ischemic and metabolic changes persisted in some patients. In a subsequent clinical study, nitrous oxide (70%) was reported to potentiate the myocardial hemodynamic and metabolic effects of isoflurane (1% end-tidal).⁷

Moffitt *et al.*⁸ evaluated isoflurane (inspired concentration range 0.67-3.8%) in patients undergoing coronary artery bypass grafting (CABG). Transient lactate production or ECG changes were detected in five of ten patients who developed tachycardia, hypertension, or elevated PCWP during induction of anesthesia with isoflurane. No correlation, however, between ischemic ECG changes and coronary sinus lactate production was observed. These changes were not present during sternotomy. These clinical studies^{6-8,16,17} indicate that isoflurane or isoflurane-nitrous oxide administration may be associated with myocardial ischemia. Myocardial blood flow maldistribution (coronary "steal") appears to occur with isoflurane, since both coronary blood flow and venous oxygen content are elevated inappropriately relative to myocardial oxygen requirements.^{6,8} Coronary vasodilation and/or marked reduction in coronary perfusion pressure appear to be responsible for regional ischemic changes during isoflurane anesthesia.

Evidence of myocardial oxygen imbalance (ECG ischemic changes, lactate production) was not detected in our patients during isoflurane-sufentanil administration. In two patients, pre-isoflurane myocardial ischemia appeared to resolve. As systemic vascular resistance decreased, M \dot{V} O₂ and oxygen extraction decreased. Coronary sinus and great cardiac vein oxygen content returned to values observed during anesthesia prior to sternotomy. No lactate production was detected in either CS or GCV blood. These findings suggest that isoflurane-sufentanil admini-

istration did not affect myocardial oxygenation under the conditions of our study. Due to the small sample size ($n = 7$) and brief period of isoflurane administration, however, our data cannot exclude the possibility that isoflurane may cause coronary vasodilation and maldistribution of blood flow leading to ischemia during other clinical circumstances (*i.e.*, prolonged administration, higher concentrations, hypotension). Furthermore, changes of myocardial blood flow and metabolism of the magnitude observed with isoflurane may be significant, but are not ruled out by the present study.

The results of the present study are not directly comparable to those of others^{6-8,16,17} because of dissimilarities in the study protocol. Nevertheless, there are several possible explanations for the discrepancy between our myocardial metabolic and electrocardiographic findings during isoflurane administration and those reported in other studies.⁶⁻⁸ In the present study, we evaluated as "control" a sufentanil-anesthetized state, whereas the other studies used awake controls. Isoflurane was administered to supplement sufentanil anesthesia, during surgical stimulation, and was titrated to restore systemic arterial pressure to pre-sternotomy values. Isoflurane was given in doses which produce no hypotension. We did not administer nitrous oxide. Our patients had normal stroke volume, low PCWP and RAP, no history of congestive heart failure, and were well premedicated and receiving beta adrenergic blocking drugs up to and including the morning of the operation. The latter may account for the slower heart rate and lower myocardial metabolic rate (*i.e.*, higher MLE) observed throughout the study period than those reported by others.^{6,7} Differences in regional coronary flow (*i.e.*, redistribution) have been found to be exaggerated as the oxygen requirement of the heart is raised by tachycardia.¹⁸

Recent studies are compatible with our findings. Hess *et al.*⁴ have shown that isoflurane can be used safely to control intraoperative hypertension in patients who had been anesthetized with fentanyl (20 mcg/kg). ECG changes in response to sternotomy, indicative of myocardial ischemia, resolved with isoflurane. Myocardial hemodynamic and metabolic evaluation, however, was not performed. Tarnow *et al.*⁵ were also unable to detect ECG evidence of myocardial ischemia with isoflurane-nitrous oxide, despite a moderate reduction in mean arterial pressure.

Potential limitations of the thermodilution method¹⁰ used to assess coronary blood flow in this study should be mentioned. The reproducibility of coronary sinus and great cardiac vein flow measurements may be affected by small positional catheter shifts due to normal cardiorespiratory cycling, Valsalva maneuvers, and surgical ma-

nipulation of the heart.^{19,20} All blood flow determinations, hemodynamic measurement, and blood sampling were made at end expiration. Other sources of potential error in global and regional coronary blood flow measurements include right atrial reflux and malposition of the thermistors against a side branch of the coronary sinus. We were careful to exclude from analysis flow tracings in which flow signal artifacts or extra systoles appeared. Initial visualization with radiographic contrast dye and comparison of continuous coronary sinus and great cardiac vein with right atrial pressure tracings enabled us to verify catheter position throughout the study.

The major finding of this study is that, when isoflurane is administered to control intraoperative increase in systemic arterial pressure and vascular resistance during sufentanil anesthesia in patients with coronary artery disease, there is no evidence of myocardial ischemia as judged by electrocardiographic ischemic changes and/or myocardial lactate production.

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