Myocardial Ischemia during Isoflurane Anesthesia: The Effect of Substituting Halothane

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Recent laboratory1-3 and clinical4-6 reports suggest that isoflurane anesthesia may be associated with myocardial ischemia. However, they also imply that the risk of ischemia is essentially confined to patients with coronary artery disease who have “steal prone” coronary anatomy or who develop tachycardia during isoflurane anesthesia. Additionally, there is no evidence that isoflurane is more likely to cause ischemia than other potent inhalation anesthetics.7,8 The case reported below demonstrates that isoflurane may cause electrocardiographic evidence of myocardial ischemia in patients at low risk for coronary artery disease and that these ECG changes may be reversed by replacing isoflurane with halothane.

REPORT OF A CASE

The patient was a 44-yr-old male, ASA physical status I, undergoing facial reconstructive surgery. He had no history of coronary artery disease, and a normal preoperative 12-lead electrocardiogram. However, he was receiving estrogen therapy as part of a “gender reidentification” program. Routine monitoring included noninvasive BP, pulse oximetry, time-shared mass spectrometry of airway gas concentrations (SARA), and five-lead electrocardiogram (Space Labs model 511, 3dB bandwidth = 0.2-50 Hz, standard AHA limb and V5 lead placement). Intermittently, when indicated by changes in the oscillographic trace, permanent recordings of the ECG (10 mm/mV scale) were made.

On arrival in the operating room, his BP was 140/90 mmHg, and his ECG was normal as shown in figure 1. After inducing anesthesia with thiopental, anesthesia was maintained with nitrous oxide, oxygen, and isoflurane. Succinylcholine was administered to facilitate tracheal intubation. Mechanical ventilation kept the end-tidal carbon dioxide tension between 25 and 30 mmHg.

Three hours later, because of persistent bleeding in the operative field, the surgeon requested that we deliberately decrease the patient’s blood pressure. Hydralazine, 10 mg iv, transiently reduced the blood pressure from 90/60 to 80/50 mmHg, while the heart rate remained stable at 90 beats/min. Thirty minutes after he received the hydralazine, (3/4 h after induction of anesthesia), the patient’s blood pressure had returned to 101/58 and his heart rate was 99 beats/min; the hemoglobin oxygen saturation was 97%, and the end-tidal isoflurane

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![ECG strips](https://example.com/figure1.png)

**FIG. 1.** Preoperative ECG (BP = 140/90 mmHg). Note that these and all subsequent ECG strips are recorded at a standard gain of 10 mm/mV. A. Lead II. B. V5.
concentration was 0.70%. At this time, 1–2 mm ST-segment depression developed in V5, as shown in figure 2; furthermore, the corrected QT interval (QTc) increased from 0.43 to 0.52 s, which also suggests myocardial ischemia.\(^6\) Isoflurane was discontinued and replaced with halothane. All other variables remained constant during the ECG recordings shown in figures 3 (23 min after isoflurane was discontinued) and 4 (44 min after isoflurane was discontinued). Note that, as the end-tidal isoflurane concentration decreased below 0.10%, the ST segments in V5 returned to their preoperative, isoelectric configuration (fig. 4B), and QTc decreased slightly to 0.50 s.

To further define the role of isoflurane in causing the observed electrocardiographic abnormality, isoflurane was reintroduced; the V5 recordings shown in figure 5A and B were recorded 2 and 6 min, respectively, after isoflurane was restarted. Heart rate and blood pressure did not change in this short interval, but ST-segment depression had already begun to reappear. Fifteen minutes after reintroducing isoflurane, the ECG tracings shown in figure 6 were recorded; at this time, the end-tidal isoflurane concentration was 0.79% and the blood pressure was stable at 94/56. Five minutes later, the ST-segment depressions had become highly significant (greater than 1 mm, downward sloping), as shown in figure 7; this was accompanied by an increase in QTc to 0.55 s. Isoflurane was therefore discontinued, this time being replaced by enflurane. Forty minutes later, the ECG recordings shown in figure 8 were made; although the end-tidal isoflurane concentration had decreased to less than 0.10%, the ST segments were still depressed in V5 and QTc had increased to 0.56 s. This was in contrast to our observations with halothane: in that case, by the time end-tidal isoflurane concentration decreased to less than 0.10%, the ST segments had returned to normal (fig. 5B). Because the ECG abnormalities did not resolve completely during enflurane anesthesia, halothane was administered for the remainder of the operative procedure; as before, the ST segments remained isoelectric during halothane administration. Postoperatively, his 12-lead electrocardiogram

was unchanged from the preoperative recording, and serial determinations of CPK isoenzymes revealed no evidence of myocardial infarction. The consulting cardiologist felt that no further evaluation was indicated.

**DISCUSSION**

This case demonstrates that isoflurane can cause ECG changes suggestive of myocardial ischemia in patients who have no history of coronary artery disease. Although the patient had received hydralazine about 30 min before his ECG abnormalities developed, it is unlikely that hydral-
azine, alone, was responsible for them; substitution of halothane for isoflurane resulted in return of the ECG pattern to normal, while reintroduction of isoflurane caused the ST-segment depression to recur. Furthermore, both substitutions took place while the patient's position, CO₂ tension, depth of anesthesia, and hemodynamic variables were reasonably stable; systolic pressures were between 94 and 101 mmHg, diastolic pressures were between 56 and 63 mmHg, and (with the exception of the data recorded during enflurane [fig. 8]) heart rates were between 99 and 103 beats/min. Therefore, it appears that, in this patient, isoflurane caused ECG changes suggestive of cardiac ischemia by a mechanism independent of its effects on heart rate and blood pressure.

The observation that enflurane was ineffective in reversing the isoflurane-induced electrocardiographic abnormalities suggests that the effects of enflurane and isoflurane on the coronary circulation differ significantly from those of halothane. In fact, Sulham demonstrated that, in rat hearts, coronary flow is significantly lower during halothane anesthesia than with equianesthetic doses of enflurane or isoflurane. This similarity between enflurane and isoflurane may be related to the fact that they are both (isomeric) halogenated ethers, while halothane is a halogenated hydrocarbon.

The role of isoflurane in the genesis of myocardial ischemia has been controversial. In uncontrolled studies of patients with known coronary artery disease, Reiz et al. found electrocardiographic and metabolic evidence of myocardial ischemia in approximately 50% of patients receiving isoflurane. Hemodynamic manipulations with phenylephrine and nitroglycerin reversed these effects in some patients, whereas substitution of narcotic-based anesthesia uniformly improved both the ECG and lactate extraction. A possible mechanism for this ischemia was suggested by Buffington et al., who demonstrated that isoflurane can decrease perfusion of collateral-dependent myocardium in dogs.

On the other hand, two large studies of patients undergoing cardiac surgery did not report an increased incidence of coronary ischemia in patients who received isoflurane as part of a balanced anesthetic technique. However, when a crossover “design” is used, it may require only a few cases to convincingly demonstrate that a difference between agents does exist. For instance, in open-chest dogs with surgically created critical coronary stenoses, Priebe found that isoflurane-induced regional wall motion abnormalities can be reversed by substitution of halothane; his sequence of isoflurane-halothane-isoflurane substitutions is reminiscent of our management of the patient described above.

The mechanism underlying the isoflurane-induced
ECG changes in this case is not clear. Although classic “coronary steal” requires two stenotic coronary vessels, transmural steal may develop with a single lesion. iso- 
flurane may have caused subendocardial ischemia by un-
masking a previously asymptomaticstenosis possibly re-
lated to my patient's estrogen intake. Had the ECG 
changes resulted from coronary spasm, they should have 
been worse with halothane (which has minimal coronary 
vasodilatory effects) than with isoflurane (a known coro-
nary dilator). Of course, it is possible that the ECG ab-
normalities we observed were indicative of repolarization 
changes caused by isoflurane (and enflurane) but unrel-
ated to cardiac ischemia. However, Reiz et al. found that 
iso- and enflurane-induced ST-segment changes are associated 
with impaired lactate extraction, which is indicative of 
coronary ischemia.

It is unclear why the ECG changes first appeared 3½ 
h after induction of anesthesia. Perhaps the effect was 
related to the duration of anesthesia, to some subtle 
change in surgical stimulation, or to the interaction of 
iso- and enflurane with the hydralazine that had been given 30 
min earlier. However, the fact that ischemic ECG 
changes were not associated with the (mild) hydralazine-
induced hypotension, and that they were reversed when 
halothane was substituted for isoflurane, suggests that 
iso- and enflurane were the primary cause of the observed ECG 
changes.

In conclusion, isoflurane caused ECG evidence of car-
diac ischemia in a patient with no history of coronary 
artery disease; substitution of halothane promptly re-
versed these changes without affecting hemodynamic 
variables, suggesting that the electrocardiographic evi-
dence of ischemia was causally related to isoflurane. 
Should such changes occur during isoflurane anesthesia, 
substitution of halothane may be an effective treatment.

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