

Changes in Ventilation, Oxygen Uptake, and Carbon Dioxide Output during Recovery from Isoflurane Anesthesia

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Recovery from inhalation anesthesia is often marked by the occurrence of postoperative tremor that resembles shivering, which is known to be associated with an increase in oxygen uptake (\dot{V}_{O_2}), CO_2 output (\dot{V}_{CO_2}), and minute ventilation (\dot{V}_E). This study determined the time course of the ventilatory changes observed during the first hour of recovery from isoflurane anesthesia. Ten patients (ASA PS 1) scheduled for minor orthopedic surgery (knee arthroscopy) were included in this study. Anesthesia was induced with thiopental (5 mg/kg) and maintained with 70% N_2O and isoflurane (1–2%) in oxygen, allowing spontaneous ventilation. In the recovery room, after N_2O had been discontinued, patients were connected to a Beckman Metabolic measurement cart®, which allowed a continuous monitoring of \dot{V}_E , \dot{V}_{O_2} , \dot{V}_{CO_2} , and PET_{CO_2} . Postoperative tremor was observed in all patients within 7.1 ± 1.2 min (mean \pm SEM) after isoflurane discontinuation and was associated with a marked increase in the following: \dot{V}_{O_2} , from 173 ± 26 ml/min at the end of anesthesia to 457 ± 88 ml/min; \dot{V}_{CO_2} , from 149 ± 18 ml/min at the end of anesthesia to 573 ± 98 ml/min; and \dot{V}_E , from 6.8 ± 0.7 l/min at the end of anesthesia to 16.6 ± 2.8 l/min (values obtained 20 min after isoflurane discontinuation). In three patients during intense shivering, \dot{V}_{O_2} , \dot{V}_{CO_2} , and \dot{V}_E reached peak values higher than 800 ml/min, 1,300 ml/min and 30 l/min, respectively. This study shows that postoperative tremor following isoflurane anesthesia may be associated with prolonged and large increases in oxygen uptake, CO_2 output, and minute ventilation. (Key words: Anesthetics, volatile: isoflurane. Carbon dioxide: output. Oxygen: uptake. Recovery. Temperature: shivering.)

RECOVERY from general anesthesia is known to be associated with marked hemodynamic and ventilatory changes related to postoperative rewarming and shivering.^{1,2} A high incidence of postanesthetic tremor has been observed following inhalation anesthesia, possibly related to hypothermia that occurs during the operative period^{3,4} or to a generalized increase in CNS activity.^{5,6} Although inhalation agents are known to depress the ventilatory responses to hypercapnia and hypoxemia in a dose-related manner,⁷ few data are available concerning the ventilatory changes during recovery from inhalation anesthesia, especially during shivering.

This study was therefore conducted to determine the time course of the changes in ventilation (\dot{V}_E), O_2 uptake (\dot{V}_{O_2}), CO_2 output (\dot{V}_{CO_2}), and temperatures that were continuously measured during the first hour following isoflurane anesthesia.

Methods

PATIENTS

Ten patients (ASA PS 1), seven males and three females (mean age, 31 yr; range, 16–52 yr; mean weight, 69 kg; range, 45–80 kg) scheduled for minor orthopedic surgery (knee arthroscopy) were included in this study after they had given written informed consent and after institutional approval was obtained.

ANESTHESIA

No premedication was given. Anesthesia was induced with thiopental (5 mg/kg) and maintained with 70% N_2O and isoflurane (1–2%) in O_2 , allowing spontaneous ventilation. Patients breathed from a nonbreathing anesthetic circuit *via* an anesthetic face mask. The surgical procedure lasted 78 ± 35 min (\pm SD). N_2O was withdrawn 10 min before the end of surgery, while FI_{O_2} was maintained at 0.3 in an air- O_2 mixture and inspired isoflurane concentration was increased to 2%. When surgery was completed, patients were sent immediately to the recovery room.

In the recovery room, patients were connected to a Beckman Metabolic measurement cart® (Sensormedics, Fullerton, California) *via* an anesthetic face mask, tightly held to the patient's face by the observer to prevent leaks. Patients were breathing spontaneously an air-oxygen mixture provided by a blender to ensure a constant concentration of inspired oxygen. FI_{O_2} was set to 0.3 during the entire study. Inspired isoflurane concentration was maintained at 2% for 20 min to obtain baseline measurements.

During each procedure the temperature of the recovery room was above 26° C. Patients were uncovered to permit observation of the onset, extent, and intensity of shivering.

METABOLIC AND VENTILATORY MEASUREMENTS

Oxygen uptake (\dot{V}_{O_2} , ml/min, STPD), carbon dioxide output (\dot{V}_{CO_2} , ml/min, STPD), tidal volume (VT, ml/

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TABLE 1. Ventilatory Variables Recorded at Control and after Isoflurane Discontinuation

	Control	10 min	20 min	35 min	45 min
\dot{V}_{O_2} (STPD ml/min)	173 ± 26	371 ± 72*	457 ± 88†	466 ± 93†	311 ± 82
\dot{V}_{CO_2} (STPD ml/min)	149 ± 18	637 ± 109†	573 ± 98†	424 ± 78†	315 ± 48*
\dot{V}_E (BTPS l/min)	6.8 ± 0.7	18.1 ± 2.7†	16.6 ± 2.8†	13.2 ± 1.6‡	11.1 ± 1.5*
PET _{CO₂} (mmHg)	39.4 ± 2.9	39.3 ± 2.0	42.0 ± 1.9	42.2 ± 1.4	39.9 ± 1.9
Pa _{CO₂} (mmHg)	51.1 ± 2.7	44.7 ± 2.5†	43.8 ± 2.0†	42.2 ± 1.4†	43.3 ± 1.6†
pH (range)	7.27 (7.19-7.31)	7.30‡ (7.26-7.36)	7.30‡ (7.25-7.36)	7.32† (7.26-7.36)	7.33† (7.27-7.39)
Pa _{O₂} (mmHg)	128.5 ± 7	139 ± 4	139 ± 6	136 ± 7	129 ± 6
V _T (ml/breath)	278 ± 32	833 ± 145†	849 ± 142†	642 ± 105‡	633 ± 100‡
F (breath/min)	25.4 ± 2.1	23.8 ± 2.8	20.4 ± 1.5*	22.0 ± 1.7	18.4 ± 1.0†

* $P < 0.05$ versus control.
† $P < 0.001$ versus control.

‡ $P < 0.01$ versus control.

breath, BTPS), respiratory rate (F, breaths/min), minute ventilation (\dot{V}_E , l/min, BTPS), and end-tidal P_{CO₂} (PET_{CO₂}, mmHg) were continuously measured during 60 min. Baseline ventilatory and metabolic measurements were performed 30 min after N₂O had been discontinued and 5 min before isoflurane discontinuation, when a steady state had been reached (as evidenced by a continuous display of \dot{V}_{O_2} , \dot{V}_{CO_2} , and \dot{V}_E). The Beckman Metabolic measurement cart[®] utilizes fast response sensors (100 ms) for the detection of oxygen and carbon dioxide partial pressure in expired breath and transducers for the measurement of temperature, pressure, and volume. Oxygen is measured with a temperature controlled polarographic sensor (Beckman OM 11 oxygen analyser[®]). Carbon dioxide is measured with a dual beam nondispersive infrared optical system with a pneumatic detector (Beckman LB₂ CO₂ analyser[®]). A turbine is used for sensing expired air volume, generating pulses as the gas flows through the transducer. The pulses are counted over time to provide an accumulative volume. The O₂ and CO₂ analyzers, as well as the temperature, pressure, and volume transducers were calibrated before each test.

Calibration. Calibration of the gas sensors was automatically accomplished with a zero gas (100% N₂) and a calibration gas (4% CO₂-36% O₂ in N₂). To calibrate the volume transducer, one manually activates a pump syringe to deliver fixed volumes at three different flow rates to the transducer. The microprocessor then performs a linearization of the volume. Automatic calibration of the pressure transducer occurs during gas calibration.

FI_{O₂} was measured (mean value, 0.26; range, 0.22-0.29) before each procedure. Oxygen uptake was calculated from the following equation⁸:

$$\dot{V}_{O_2} = \left[FI_{O_2} \times \left[\frac{1 - FE_{O_2} - FE_{CO_2}}{1 - FI_{O_2}} \right] - FE_{O_2} \right] \times \dot{V}_E$$

Carbon dioxide output was measured as

$$\dot{V}_{CO_2} = \dot{V}_E \times FE_{CO_2}$$

where FI_{O₂} = inspired oxygen concentration, FE_{O₂} = oxygen concentration in the mixed expired gas, FE_{CO₂} = CO₂ concentration in the mixed expired gas, and \dot{V}_E = expired minute volume. The accuracy of the Beckman Metabolic measurement cart[®] was validated as described by others.^{9,10} Therefore, under the conditions of the study (FI_{O₂} < 0.3), we expected an accuracy of ± 5% in the measurement of \dot{V}_{O_2} .

Heart rate and arterial blood pressure were continuously monitored *via* a Hewlett-Packard noninvasive blood pressure monitor (783 52 A[®]), which provides accurate measurements in shivering patients by rejecting artifacts. Rectal temperature (RT) was displayed continuously on a Hewlett-Packard temperature module by means of a thermistor probe inserted 10 cm into the rectum. Skin thermistor probes were fixed with plastic tape on the chest, upper arm, anterior mid thigh, and lateral mid calf. Mean skin temperature (MST) was calculated according to Ramanathan's formula: MST = 0.3 (T° chest + T° arm) + 0.2 (T° thigh + T° calf).¹¹

Arterial blood gases (IL 1302 Instrumentation Laboratory System, Milan), and temperatures were recorded 5 min before isoflurane discontinuation for baseline measurements and 10, 20, 35, and 45 min thereafter. Serum lactate concentrations (Dupont's Instruments Automatic clinical analyser ACA III[®], Wilmington, Delaware)¹² were measured when intense shivering was observed. For technical reasons, these measurements were not performed in two patients.

STATISTICS

All values are expressed as mean ± SEM. Statistical analysis was performed using a two-way analysis of variance. $P < 0.05$ was considered significant.

Results

The results of temperature recordings, ventilatory and hemodynamic variables, and blood gas analysis are given in tables 1 and 2.

TABLE 2. Temperatures and Hemodynamic Variables Recorded at Control and after Isoflurane Discontinuation

	Control	10 min	20 min	35 min	45 min
RT (° C)	35.3 ± 0.2	35.3 ± 0.2	35.5 ± 0.2	35.8 ± 0.2*	36.2 ± 0.2*
MST (° C)	31.9 ± 0.2	32.2 ± 0.2	32.5 ± 0.1†	33.2 ± 0.2*	33.6 ± 0.2*
MAP (mmHg)	76 ± 3.8	103 ± 5.2*	105 ± 4.6*	104 ± 4.7*	101 ± 5.4*
HR (beats/min)	94 ± 3.2	104 ± 6.6	97 ± 4.9	95 ± 4.0	92 ± 4.1

* $P < 0.001$ versus control.

† $P < 0.01$ versus control.

At the onset of the study, all patients were hypothermic (RT = 35.3 ± 0.2° C). Postoperative tremor that resembled shivering was observed in all patients within 7.1 ± 1.2 min after isoflurane discontinuation, and lasted 20 min approximately. As described before,¹³ there was a progressive involvement of the muscles of the neck, abdominal and pectoral regions, and finally of the lower limbs. In all experiments, determination of the occurrence of generalized shivering was made by the same observer.

Compared with the anesthesia state, postoperative tremor was associated with a marked increase in \dot{V}_{O_2} , \dot{V}_{CO_2} , and \dot{V}_E , as shown in figures 1 and 2. In the three patients who had the highest peak values in \dot{V}_{O_2} (>800 ml/min) and \dot{V}_{CO_2} (>1,300 ml/min), minute ventilation reached 36 l/min, 35.7 l/min, and 30 l/min, respectively. Moreover, these ventilatory changes remained highly significant 35 min after isoflurane discontinuation. In four of ten patients, \dot{V}_E remained above 20 l/min during more than 15 min. The increase in \dot{V}_E resulted mainly from an increase in VT rather than an increase in respiratory rate. No hypoxemia was observed throughout the study. In all patients, PaO₂ remained above 120 mmHg during intense shivering. During the first 10 min of recovery, while \dot{V}_E increased from 6.8 ± 0.7 l/min to 18.1 ± 2.7 l/min, PaCO₂ decreased from 51.1 ± 2.7 mmHg to 44.7 ± 2.5 mmHg. During the following period, PETCO₂ and PaCO₂ remained unchanged, whereas \dot{V}_{CO_2} was still markedly increased (fig. 2).

There was a significant increase in mean arterial pressure (MAP) ($P < 0.001$) during the period of generalized shivering with no appreciable change in heart rate (table 2).

Some patients complained of discomfort during shivering, but none of them complained of pain, and they did not receive analgesics during the study period.

Serum lactate concentrations could be measured during intense shivering in eight of ten patients only. In three patients who developed violent shivering, lactate levels reached 4.1 mmol/l, 3.9 mmol/l, and 2.8 mmol/l, respectively (normal value in arterial blood = 0.5 to 1.6 mmol/l) (table 3).

Discussion

Recovery from anesthesia is often marked by postoperative tremor that resembles shivering, although its incidence varies considerably with the combination of anesthetic agents used. Shivering has been observed most frequently following inhalation anesthesia, and reports of its incidence following halothane, enflurane, or isoflurane anesthesia have varied from 21% to 66%.³⁻⁵ Although the relationship between hypothermia and shivering has been much debated,^{1-4,14-16} the rapid elimination of isoflurane might explain the sudden recovery of thermoregulatory mechanisms.^{17,18} However, during awakening from anesthesia, postoperative tremor is frequently associated with transient abnormal neurologic reflexes, such as sustained ankle clonus and upgoing plantar responses, especially after enflurane anesthesia.⁵ More recently, Sessler *et al.* have suggested that postoperative tremor could

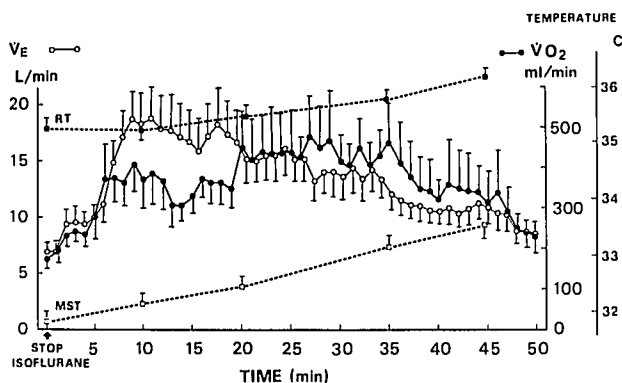


FIG. 1. Mean values ± SEM of rectal temperature (RT), mean skin temperature (MST), minute ventilation (\dot{V}_E), and oxygen uptake (\dot{V}_{O_2}), after isoflurane discontinuation.

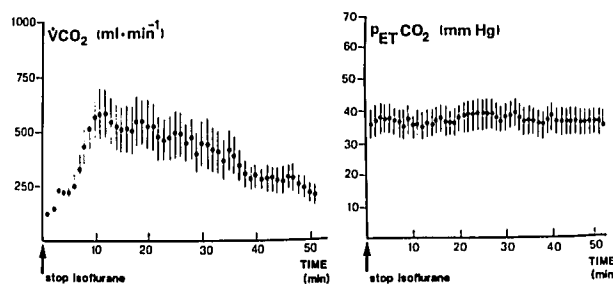


FIG. 2. Mean values ± SEM of CO₂ output (\dot{V}_{CO_2}) and end-tidal P_{CO₂} (PETCO₂) after isoflurane discontinuation.

TABLE 3. Lactate Levels at the Peak of Shivering (20 Min after Isoflurane Discontinuation)

Patient No.	Sex	Body Surface Area (m ²)	Age (yr)	Lactate (mmol/l)
1	Female	1.50	44	1.6
2	Male	1.96	29	4.1
3	Male	1.96	52	3.9
4	Female	1.68	37	—
5	Male	2.00	40	—
6	Female	1.44	16	1.9
7	Male	2.08	24	2.8
8	Male	2.08	17	1.5
9	Male	1.94	26	1.2
10	Male	1.89	26	1.2

result from a depression of supraspinal inhibitory pathways by residual anesthetics, thereby leading to increased spinal reflex activity.⁶

The muscle hyperactivity of shivering increases markedly the metabolic demand, which results in an increased pulmonary ventilation and cardiac output.² However, the increased oxygen uptake commonly observed during the recovery period may also result from the increased metabolism involved in paying off the heat debt developed during the period of cold exposure (nonshivering thermogenesis).^{13,19} Furthermore, Waxman *et al.*²⁰ have also suggested that the increased oxygen uptake observed during the recovery period might result from the metabolic debt accumulated intraoperatively from inadequate tissue oxygenation.

In the present study, all patients were hypothermic (RT = 35.3 ± 0.2° C) when they were admitted in the recovery room. To observe carefully the onset and extent of shivering, patients were uncovered. Although the temperature of the recovery room was maintained above 26° C during each procedure, the occurrence of shivering might have been increased by patients' total exposure during the immediate postoperative period.

The continuous monitoring of ventilation allowed us to better describe the time course of the ventilatory changes. Bay *et al.*² have already shown that postoperative tremor was associated with an increased metabolic demand. However, the maximal change in minute ventilation, \dot{V}_{O_2} , and \dot{V}_{CO_2} might have been underestimated in their study because of discontinuous measurements.

In the present study, the mean increase in \dot{V}_{O_2} reached 230 ± 91% when compared with the state of anesthesia. However, oxygen uptake is known to be decreased during anesthesia.^{21,22} Thus, when compared with normal resting awake values,²³ the mean increase in \dot{V}_{O_2} was found to be only 80%. Nevertheless, in three of ten patients who developed violent postoperative tremor, we observed a 200% increase in \dot{V}_{O_2} above normal awake values.

Calculation of oxygen uptake can be modified by the presence of anesthetic gases in the inspired and the mixed

expired gas.⁸ During baseline measurements, inspired isoflurane concentration (FI isoflurane) was 2%; thus, isoflurane concentration in the mixed expired gas (FE isoflurane) could be estimated to be close to 1.6%.²⁴ Therefore, calculation of oxygen uptake by the Beckman Metabolic measurement cart[®] was slightly underestimated by ignoring isoflurane concentration in both the inspired and the mixed expired gas (maximal $\Delta\dot{V}_{O_2} = 9.5 \pm 1.3$ ml/min). During the first minutes following isoflurane discontinuation, calculation of oxygen uptake might have been overestimated by ignoring FE isoflurane (maximal $\Delta\dot{V}_{O_2} = 37 \pm 5.3$ ml/min).

In the present study, we observed a marked increase in the alveolar-arterial difference for CO₂ (P(A-a)CO₂) during isoflurane anesthesia, whereas this gradient decreased rapidly after isoflurane discontinuation. This increase in P(A-a)CO₂ may be explained by the low tidal volume ($V_T = 278 \pm 32$ ml) and the increased respiratory dead space resulting from prolonged isoflurane anesthesia.²⁵

From the data of Farhi and Rahn,²⁶ it may be assumed that a 1 mmHg decrease of P_{CO₂} should release approximately 120 ml of CO₂ from the body stores. Thus, during the first 10 min of hyperpnea, the decrease in Pa_{CO₂} from 51.1 ± 2.7 mmHg to 44.7 ± 2.5 mmHg reflects the elimination of CO₂ accumulated during the preceding period of isoflurane-induced ventilatory depression. However, during the following period P_{ET}CO₂ and Pa_{CO₂} remained unchanged, whereas \dot{V}_{CO_2} was still markedly increased. The constant Pa_{CO₂} suggests that ventilation was perfectly accommodated to the increased CO₂ production resulting from postoperative tremor. This finding is of particular interest because it has been found that low concentrations of isoflurane (0.1 MAC) expected during the first hour of recovery from isoflurane anesthesia⁶ could induce a marked depression of peripheral chemosensitivity.^{7,27}

Abdul-Rasool *et al.*²⁸ have also recently shown that the ventilatory response to the increased metabolic production of CO₂, resulting from electrically induced leg exercise in anesthetized dogs, was not impaired by increasing concentrations of enflurane, despite a dose-dependent decrease in the slope of the ventilatory response to CO₂ (\dot{V}_E/Pa_{CO_2}). Moreover, Stremel *et al.*²⁹ found that venous CO₂ loading (which can be produced by muscular exercise or shivering) in awake spontaneously breathing dogs resulted in an isocapnic hyperpnea that was significantly greater than the hypercapnic hyperpnea resulting from airway CO₂ loading. They concluded that the rate of CO₂ flow to the lungs was linked to ventilatory regulation as a ventilatory stimulus not mediated by significant changes in mean arterial P_{CO₂}. This concept that ventilation and CO₂ output are closely matched has been much debated in other studies using awake, anesthetized, or decerebrate animals.³⁰

Depletion of the CO₂ stores throughout the period of hyperpnea might explain the elevated gas exchange ratio (RQ > 0.90)^{23,31} and the discrepancy between V_{O₂} and V_{CO₂} observed in our study during the 20-min period of postoperative tremor. Moreover, in the three shivering patients who had elevated lactate values, at least part of the increase in RQ might be explained by the buffering of lactic acid produced by the anaerobic breakdown of glycogen in the working muscles.³²⁻³⁵

In conclusion, the results of our study demonstrate that postoperative tremor following isoflurane anesthesia may be associated with prolonged and large increases of oxygen uptake and carbon dioxide output. Nevertheless, all patients had evidence of adequate ventilation with rapid normalization of arterial CO₂ tension despite the prolonged elevation of CO₂ output. The significance of these results remains to be clarified in the patient with limited cardiopulmonary reserve.

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