

## ***Increases in Hemodynamic Variables and Catecholamine Levels after Rapid Increase in Isoflurane Concentration***

Arvi Yli-Hankala, M.D., Ph.D.,\* Tarja Randell, M.D., Ph.D.,\* Timo Seppälä, M.D., Ph.D.,†  
Leena Lindgren, M.D., Ph.D.‡

**Background:** Ventilation of the lungs with isoflurane in nitrous oxide and oxygen has been shown to increase the plasma concentration of norepinephrine. Whether this increase is related to the tachycardia and increased arterial blood pressures, seen following a sudden increase in the concentration of isoflurane, was tested in humans.

**Methods:** Twenty-two healthy patients in whom the trachea was intubated were given 15 min of stable isoflurane-O<sub>2</sub>-air anesthesia [end-tidal concentration of isoflurane (ET<sub>iso</sub>) of 1.3%] (baseline). Patients were then randomly allocated to one of two groups. For 13 "Iso<sub>high</sub>" patients, the inspired concentration of isoflurane was increased abruptly. In those patients, the ET<sub>iso</sub> was kept at 2.6% for 10 min, *i.e.*, until the end of the study, after which the depth of anesthesia was reduced. For nine "Iso<sub>low</sub>" control patients, the ET<sub>iso</sub> level of 1.3% was continued until the end of the study. Heart rate, arterial pressures, catecholamine levels, and end-tidal concentration of CO<sub>2</sub> were recorded at baseline and at 1, 1.5, 2, 4, 6, and 10 min after increase in isoflurane.

**Results:** Iso<sub>high</sub> patients showed significant increases in heart rate (40%, from 84.6 to 118.1 beats/min), systolic arterial pressure (SAP, 23%, from 96.4 to 118.3 mmHg), and diastolic arterial pressure (DAP, 30%, from 53.9 to 70.0 mmHg); all three variables peaked at 2 min. Significant increases occurred also in norepinephrine levels (80%, from 0.342 to 0.615 ng/ml) and in end-tidal concentration of CO<sub>2</sub> (from 4.22% to 4.43%), both of which peaked at 4 min. Epinephrine levels did not increase significantly, although significant differences were

seen between Iso<sub>high</sub> and Iso<sub>low</sub> patients during the trial. Iso<sub>low</sub> patients had no changes in these variables.

**Conclusions:** A sudden increase in isoflurane concentration is associated with a transient but clinically significant increase in heart rate, arterial pressures, and norepinephrine concentration. (Key words: Anesthetics, volatile: isoflurane. Heart: tachycardia. Sympathetic nervous system: catecholamines; epinephrine; norepinephrine.)

ISOFLURANE is known to increase heart rate (HR),<sup>1</sup> causing significant tachycardia during induction of anesthesia given by face mask to children.<sup>2</sup> After induction with thiopental, and then ventilation with isoflurane, nitrous oxide, and oxygen by mask, the plasma concentration of norepinephrine increases in adults.<sup>3</sup> Plasma levels of catecholamines are increased during isoflurane-induced controlled hypotension, when opioid analgesics are not used.<sup>4</sup> With opioids, stable isoflurane anesthesia used for controlled hypotension does not increase plasma catecholamines.<sup>5</sup>

In our experience, when the isoflurane concentration is increased rapidly in adults, tachycardia and an increase in arterial pressures often ensue. This phenomenon may be associated with catecholamine release. Therefore, we studied the effect of an increase in isoflurane concentration on hemodynamic variables and catecholamine levels in healthy patients. Patients receiving a constant level of isoflurane served as controls.

### **Patients and Methods**

Twenty-two ASA physical status 1 patients undergoing elective minor surgery participated in the study (table 1). The Ethics Committee of the Fourth Department of Surgery approved the study protocol, and each patient provided written informed consent.

#### **Anesthesia**

Oxazepam, 15–30 mg orally, was given the night before surgery, and diazepam, 0.2 mg/kg orally, 90 min

\* Staff Anesthesiologist, Department of Anesthesiology, Fourth Department of Surgery.

† Professor of Pharmacology and Toxicology, Department of Biochemistry, National Public Health Institute, Helsinki, Finland.

‡ Associate Professor of Anesthesiology, Department of Anesthesiology, Fourth Department of Surgery.

Received from the Department of Anesthesiology, Fourth Department of Surgery, Helsinki University Central Hospital, Helsinki, Finland. Accepted for publication October 22, 1992. Supported in part by a grant from the Academy of Finland. Presented in part at the 10th World Congress of Anesthesiologists, The Hague, The Netherlands, June 12–19, 1992.

Address reprint requests to Dr. Yli-Hankala: Department of Clinical Sciences, University of Tampere, P.O. Box 607, SF-33101 Tampere, Finland.

## ISOFLURANE AND CATECHOLAMINES

Table 1. Patient Characteristics

Group	N	Sex (M/F)	Age* (yr)	Weight* (kg)	Height* (cm)
Iso <sub>High</sub>	13	5/8	31 ± 9	68 ± 15	170 ± 13
Iso <sub>Low</sub>	9	4/5	30 ± 8	68 ± 15	173 ± 8

\* Values are mean ± SD.

before anesthesia. In the operating room, a peripheral intravenous catheter was inserted into a cubital vein. A radial artery was cannulated for continuous monitoring of arterial pressures (Cardiicap Ultima<sup>®</sup>, Datex, Finland). A basilic vein was cannulated, and a 70-cm catheter was introduced into the right ventricle of the heart (location verified by pressure waveform, Cardiicap Ultima<sup>®</sup>). We applied local anesthetic cream (EMLA<sup>®</sup>, Astra, Sweden) to all puncture sites 90 min before cannulations. Patients rested for 20 min after cannulations. Continuous monitoring of lead CB<sub>5</sub> of the electrocardiogram was started. The electrocardiogram was printed out throughout the study period, and hemoglobin oxygen saturation (SpO<sub>2</sub>) by pulse oximetry was recorded.

We administered 2.5 mg/kg propofol for induction of general anesthesia and 0.1 mg/kg vecuronium to provide muscle relaxation. No anticholinergic drug was given. After tracheal intubation, the lungs were ventilated mechanically with a mixture of oxygen and air at a fractional inspired concentration of oxygen of 0.35. We used a semi-open circuit system (Servo<sup>®</sup> 900 B ventilator, Siemens Elema, Sweden) at a fresh gas flow of 10L/min. Maintenance of anesthesia consisted of administration of isoflurane sufficient to produce an end-tidal concentration of isoflurane (ET<sub>Iso</sub>) of 1.3% and mild hypocapnia end-tidal concentration of carbon dioxide (ET<sub>CO<sub>2</sub></sub>) of 4.2%, (Cardiicap Ultima<sup>®</sup>). For each patient, the gas monitor was calibrated with a known concentration of CO<sub>2</sub> (5.0 vol%) and enflurane (3.0 vol%; Quick Cal<sup>™</sup> <sup>®</sup>, Datex, Finland). After stable isoflurane anesthesia for 15 min (baseline), patients were allocated randomly to one of two groups.

For 13 "Iso<sub>High</sub>" patients, we increased the inspired concentration of isoflurane to 5%, the goal being to produce an ET<sub>Iso</sub> of 2.6%. The end-tidal level of 2.6% was maintained until the end of the study by adjusting the vaporizer setting, when necessary. Heart rate, SAP and DAP, and ET<sub>CO<sub>2</sub></sub> were recorded at baseline and at 1, 1.5, 2, 4, 6, and 10 min after increasing the concentration of isoflurane. After 10 min, depth of anesthesia was lightened. For the other nine patients (the

"Iso<sub>Low</sub>" group, controls), ET<sub>Iso</sub> was kept at 1.3%, and the same variables were recorded at parallel time. The study was completed before surgery. For determination of catecholamine levels, mixed venous blood samples were drawn from the right ventricle of the heart at these same time points and were placed in prechilled tubes containing ethylenediaminetetraacetic acid (EDTA). The samples were immersed immediately in ice, centrifuged at 0° C, and stored at -70° C.

#### Catecholamine Assay

Plasma concentrations of norepinephrine and epinephrine were determined in duplicates by high-pressure liquid chromatography using electrochemical detection (ESA Coulochem 5100A, Bedford, MA). The method is a modification from Seppälä *et al.*<sup>6</sup> Catecholamines were extracted with activated aluminum (Merck, Darmstadt, Germany), and dihydroxybenzamine was used as an internal standard. The aqueous mobile phase contained 0.03 mol/l of monochloroacetic acid, 0.03 mol/L of Na<sub>3</sub>PO<sub>4</sub>, 120 mg/L of octanysulphonic acid, and 25 mg/L of Na-EDTA (pH 2.55, adjusted with phosphoric acid). A reversed-phase Zorbax ODS C<sub>18</sub> column (Rockland Tech., Newport, DE) was used. Detection limits for norepinephrine and epinephrine were 0.03 and 0.015 ng/ml, respectively. The method has intra-assay coefficients of variation of approximately 4% for norepinephrine and 10% for epinephrine in the physiologic concentration ranges.

#### Statistical Analyses

Data were analyzed using Wilcoxon matched-pairs, signed-rank test to compare differences within groups, and the Mann-Whitney-U test to compare differences between groups. Regression analysis was drawn for the relationship between the changes in catecholamine concentrations and hemodynamic parameters. Data are presented as means ± SD. A *P* value less than .05 was considered statistically significant.

#### Results

The study groups were comparable with regard to sex, age, weight, and height (table 1). By 2 min after abrupt increase in isoflurane, ET<sub>Iso</sub> had increased to 2.5 ± 0.16% in Iso<sub>High</sub> patients.

Figures 1-3 show that hemodynamic variables increased significantly in Iso<sub>High</sub> patients, peak values occurring at 2 min: compared with baseline, HR increased 40%; SAP, 23%; and DAP, 30%, on average. (For one Iso<sub>High</sub> patient, HR increased from 87 to 160 beats/min

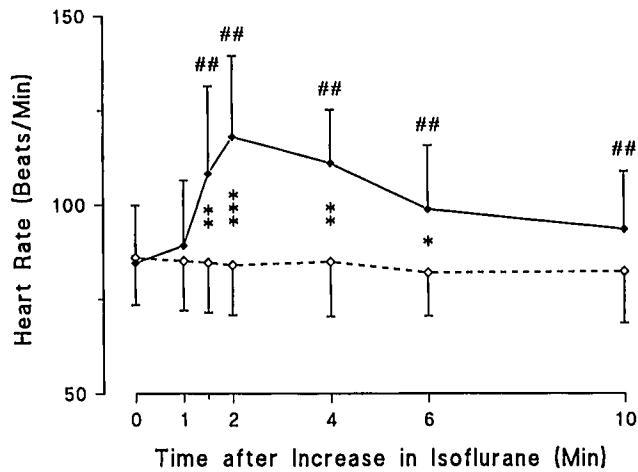


Fig. 1. Heart rate at six time points for 22 patients given one of two levels of isoflurane. Both groups first had 15 min of stable isoflurane anesthesia end-tidal concentration (ET<sub>iso</sub>) of 1.3%; the end of this period is represented by 0 on the time scale (baseline). Nine control patients (the Iso<sub>Low</sub> group, ◇---◇) continued receiving this constant level of isoflurane for 10 min more, i.e., until the end of the study. Thirteen other patients (the Iso<sub>High</sub> group, ◆—◆) had an abrupt increase in the inspired concentration of isoflurane, the goal being to produce an ET<sub>iso</sub> of 2.6%. Ten minutes later, anesthesia was lightened. Values are means ± SD. Differences between groups were significant at the following *P* levels: <.05, \* <.01, \*\* and <.001, \*\*\* as determined by the Mann-Whitney U test. Differences within the Iso<sub>High</sub> group from baseline were significant at *P* <.01, ## as determined by Wilcoxon matched-pairs signed-rank test.

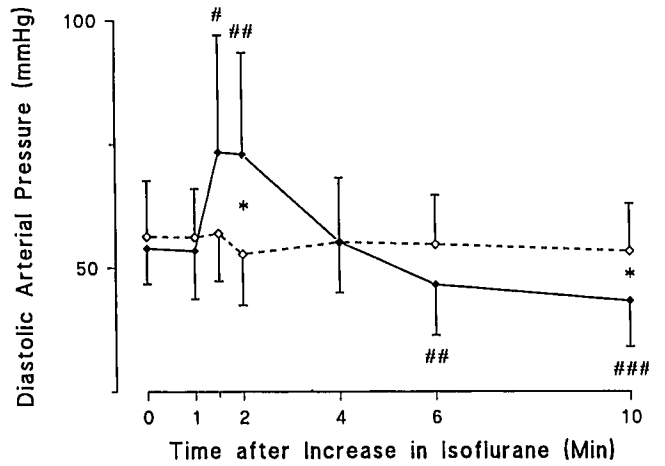


Fig. 3. Diastolic arterial pressure for Iso<sub>High</sub> and Iso<sub>Low</sub> patients (see legend for fig. 1). Differences between groups were significant at *P* <.05. \* Differences within the Iso<sub>High</sub> group from baseline were significant at the following *P* levels: <.05, # <.01, ## and <.001, ###

and arterial pressures from 124/64 to 171/105 mmHg.) Iso<sub>Low</sub> patients had no change in hemodynamic variables (figs. 1–3). Except for the sinus tachycardia in Iso<sub>High</sub> patients, no cardiac arrhythmias were discernible in any patient.

Changes in catecholamine levels are shown in figures 4 and 5. For Iso<sub>High</sub> patients, epinephrine levels were highest at the 2-min recording, but the change from baseline was not statistically significant. The plasma epinephrine concentrations did correlate, however,

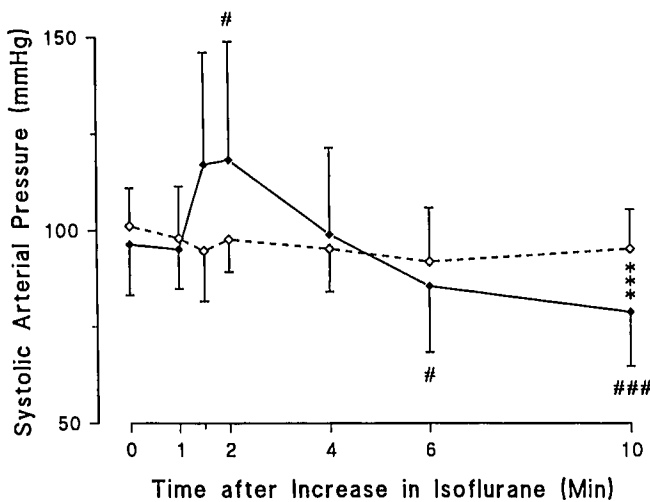


Fig. 2. Systolic arterial pressure for Iso<sub>High</sub> and Iso<sub>Low</sub> patients (see legend for fig. 1). Differences between groups were significant at *P* <.001, \*\*\* Differences within the Iso<sub>High</sub> group from baseline were significant at the following *P* levels: <.05# and <.001, ###

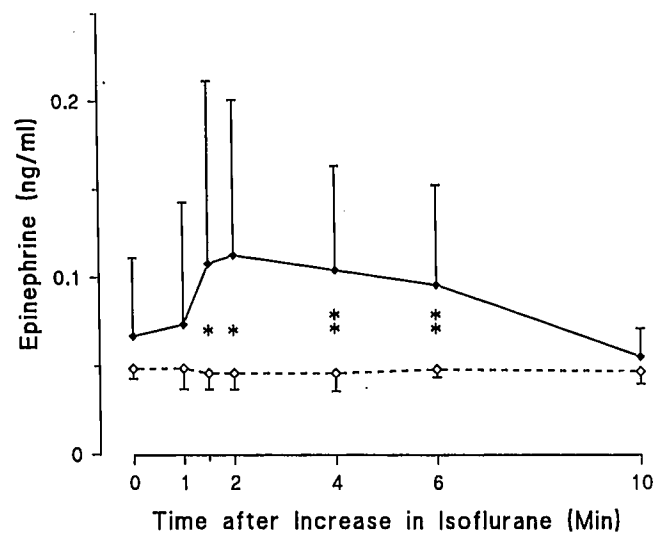


Fig. 4. Plasma epinephrine levels for Iso<sub>High</sub> and Iso<sub>Low</sub> patients (see legend for fig. 1). Differences between groups were significant at the following *P* levels: <.05\* and <.01.\*\*

## ISOFLURANE AND CATECHOLAMINES

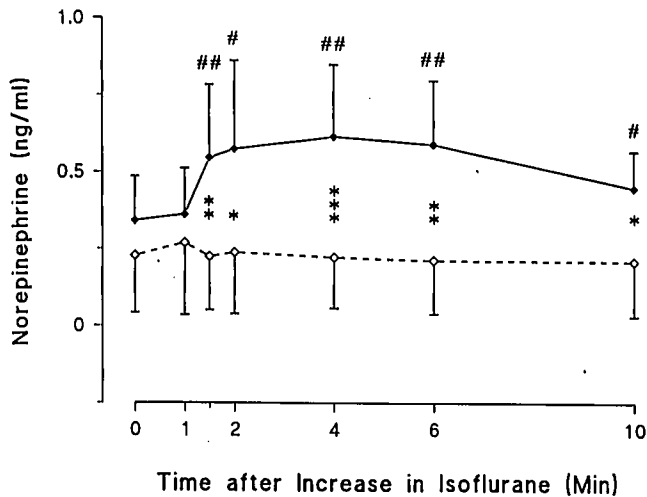


Fig. 5. Plasma norepinephrine levels for Iso<sub>High</sub> and Iso<sub>Low</sub> patients (see legend for fig. 1). Differences between groups were significant at the following *P* levels: <.05,\* <.01,\*\* and <.001,\*\*\*. Differences within the Iso<sub>High</sub> group from baseline were significant at the following *P* levels: <.05# and <.01.##

with the increase in HR ( $r = 0.6909$ ,  $P < .05$ ; table 2). Iso<sub>Low</sub> patients had no change in epinephrine levels. The difference between mean values of epinephrine in the two groups was significant in data points from 1.5 to 6 min. In Iso<sub>High</sub> patients, norepinephrine levels were highest at the 4-min recording, and the increase (80%) was significant ( $P < .01$ ). This increase correlated well with changes in arterial pressures (table 2). In Iso<sub>Low</sub> patients, the plasma norepinephrine levels remained stable, and the difference between the two groups was significant in data points from 1.5 to 10 min.

Table 3 shows  $ET_{CO_2}$  and  $SpO_2$  during the trial. For Iso<sub>High</sub> patients,  $ET_{CO_2}$  increased from  $4.22 \pm 0.51\%$  to its maximum,  $4.43 \pm 0.58\%$  ( $P < .01$ ), at 4 min and decreased to  $4.27 \pm 0.46\%$  at 10 min. Increases in  $ET_{CO_2}$  were associated with increases in plasma concentrations of epinephrine ( $r = 0.5596$ ,  $P < .05$ ). For Iso<sub>Low</sub> patients,  $ET_{CO_2}$  varied from 4.13% to 4.24%.  $SpO_2$  remained above 94% for every patient throughout the study.

## Discussion

The present study shows that when depth of isoflurane anesthesia is increased abruptly, HR, arterial pressures, and plasma concentrations of norepinephrine also increase. These changes did not occur in control patients given a stable concentration of isoflurane.

Isoflurane anesthesia is associated with marked va-

sodilatation,<sup>7,8</sup> which, under normal conditions, is compensated for by tachycardia. There are several explanations regarding the cause of tachycardia. Some believe that the baroreflex function is almost normal during isoflurane anesthesia.<sup>9</sup> At the least, baroreflex function is depressed during isoflurane anesthesia,<sup>10</sup> but less so than during enflurane or halothane anesthesia.<sup>11</sup> In this study, baroreflex activation would not seem likely since arterial blood pressure also was increased. Another possible explanation for tachycardia is beta-sympathomimetic activation: because isoflurane depresses parasympathetic activity to a greater extent than sympathetic activity, sympathetic function remains more intact and causes tachycardia.<sup>12</sup>

The mechanism of sympathoadrenal activation in our study is not clear. Isoflurane is an irritating vapor,<sup>13</sup> producing laryngospasm and breath-holding in pediatric patients during induction of anesthesia by face mask.<sup>14</sup> In a recent study by Nishino *et al.*,<sup>15</sup> nasal insufflation of 5% enflurane, isoflurane, or halothane were associated with prolongation of expiratory time of spontaneous ventilation, and an increase in laryngeal wall tension. Topical lidocaine applied to the nasal mucosa abolished these airway reflexes. Coleridge *et al.*<sup>16</sup> have shown that high concentrations of halothane, ether, chloroform, or trichloroethylene produce an immediate excitation of pulmonary stretch receptors, followed by a marked depression of receptor activity. Unfortunately, they did not report the changes in hemodynamics. In the present study, the receptors of upper airways were passed using tracheal intubation. Lungs, however, are rich in sensory afferent nerve endings, some of which may be the source of sympathoadrenal reflex responses presented here.

The results obtained in the present study are in accordance with our earlier findings,<sup>3</sup> *i.e.*, that ventilation by mask with isoflurane in nitrous oxide and oxygen increased the plasma concentration of norepinephrine.

Table 2. Correlations between Catecholamine Plasma Concentrations and Hemodynamic Parameters from Baseline to 2 min in Patients in Whom the Isoflurane Concentration Was Increased Abruptly

	Correlation ( <i>r</i> )	<i>P</i>
Epinephrine vs. HR	0.6909	<.05
Norepinephrine vs. SAP	0.8273	<.01
Norepinephrine vs. DAP	0.8412	<.001

HR = heart rate; SAP = systolic arterial pressures; DAP = diastolic arterial pressures.

**Table 3. ET<sub>CO<sub>2</sub></sub> and Hemoglobin Oxygen Saturation for Iso<sub>High</sub> and Iso<sub>Low</sub> Patients\***

	Baseline	Time after Abrupt Increase in Concentration of Isoflurane (min)					
		1	1.5	2	4	6	10
ET <sub>CO<sub>2</sub></sub> (%)							
Iso <sub>High</sub>	4.22 ± 0.51	4.25 ± 0.50	4.26 ± 0.53	4.32 ± 0.54†	4.43 ± 0.58‡	4.40 ± 0.53†	4.27 ± 0.46
Iso <sub>Low</sub>	4.24 ± 0.34	4.2 ± 0.33	4.21 ± 0.31	4.23 ± 0.36	4.19 ± 0.36	4.18 ± 0.36	4.13 ± 0.33
SpO <sub>2</sub> (%)							
Iso <sub>High</sub>	98 ± 1.0	98.3 ± 0.9	98.5 ± 0.7	98.3 ± 0.8	98.3 ± 0.8	97.9 ± 1.2	97.9 ± 1.5
Iso <sub>Low</sub>	97.4 ± 0.9	97.4 ± 0.9	97.3 ± 1.0	97.2 ± 1.1	97.3 ± 1.0	97.4 ± 0.9	97.4 ± 0.9

Values are mean ± SD.

ET<sub>CO<sub>2</sub></sub> = end-tidal concentration of carbon dioxide; SpO<sub>2</sub> = hemoglobin oxygen saturation.

\* Twenty-two surgical patients were given 15 min of stable isoflurane anesthesia [end-tidal concentration of isoflurane (ET<sub>iso</sub>) of 1.3%]; the end of this period is baseline. Then, for nine of these patients (the control Iso<sub>Low</sub> group), isoflurane was continued at this level for 10 more min. The other 13 patients (the Iso<sub>High</sub> group) were given an abrupt increase in isoflurane, the goal being to produce an ET<sub>iso</sub> of 2.6%. Ten minutes later, isoflurane was decreased.

†  $P < .05$  versus baseline (as determined by Wilcoxon's test).

‡  $P < .01$  versus baseline (as determined by Wilcoxon's test).

Nitrous oxide has been shown to augment sympathetic outflow,<sup>17</sup> and nitrous oxide also decreases removal of norepinephrine from the pulmonary circulation.<sup>18</sup> Our previous results may be influenced at least partly by nitrous oxide. In the present study, however, nitrous oxide was not used. These results are also similar to those from a recent paper in which HR and arterial blood pressure increased in patients breathing high inspired concentrations of desflurane.<sup>19</sup>

The method used here was unusual and specific to this particular study. The responses seen in these patients may not be the same in patients who have received opioids,<sup>5</sup> nitrous oxide,<sup>17,18</sup> or other drugs. We used a semi-open circuit anesthesia system to evaluate the phenomenon. The concentration of isoflurane would have changed more slowly with a semi-closed system (low fresh gas flow), and the sympathoadrenal response presented here might have been smaller. Also, to avoid the increases in plasma levels of catecholamines caused by hypercarbia,<sup>20</sup> the lungs of our patients were hyperventilated slightly. ET<sub>CO<sub>2</sub></sub> increased in Iso<sub>High</sub> patients (maximum value at 4 min), likely reflecting the increase in cardiac output,<sup>21</sup> in turn associated with the catecholamine release.<sup>22</sup> No patient became hypercarbic or hypoxic during the study.

The lungs selectively take up catecholamines, especially norepinephrine, to a significant extent.<sup>23,24</sup> Derbyshire *et al.*<sup>25</sup> observed higher concentrations of catecholamines in central venous blood than in arterial or peripheral venous blood. Therefore, to determine the level of these substances in plasma, we took samples of mixed venous blood from the right ventricle of the heart.

In conclusion, rapid increase in the inspired concentration of isoflurane causes sympathoadrenal activation and an associated hemodynamic response. This sequence could be misinterpreted by a clinician who expects deepening of anesthesia but sees, instead, an increase in HR, arterial pressures, and ET<sub>CO<sub>2</sub></sub>. We believe that activation of sympathoadrenal system may be caused by the irritating effect of isoflurane on the airways. Also, an unknown autonomic control mechanism may be involved.

## References

1. Eger EI II: Isoflurane: A review. *ANESTHESIOLOGY* 55:559-567, 1981.
2. Lindgren L, Randell T, Saarnivaara L: Comparison of inhalation induction with isoflurane or halothane in children. *Eur J Anaesthesiol* 8:33-37, 1991
3. Randell L, Seppälä T, Lindgren L: Isoflurane in nitrous oxide and oxygen increases plasma concentrations of noradrenaline but attenuates the pressor response to intubation. *Acta Anaesthesiol Scand* 35:600-605, 1991
4. Bernard JM, Pinaud M, Macquin-Mavier I, Remi JP, Souron R, Bainvel JV: Impact of surgical stress on the haemodynamic profile of isoflurane-induced hypotension. *Acta Anaesthesiol Scand* 32:248-252, 1988
5. Macnab MSP, Manninen PH, Lam AM, Gelb AW: The stress response to induced hypotension for cerebral aneurysm surgery: A comparison of two hypotensive techniques. *Can J Anaesth* 35:111-115, 1988
6. Seppälä T, Scheinin M, Capone A, Linnoila M: Liquid chromatographic assay for CSF catecholamines using electrochemical detection. *Acta Pharmacol Toxicol* 55:81-87, 1984
7. Stevens WC, Cromwell TH, Halsey MJ, Eger EI II, Shakespeare TF, Bahlman SH: The cardiovascular effects of a new inhalation anesthetic, Forane, in human volunteers at constant arterial carbon dioxide tension. *ANESTHESIOLOGY* 35:8-16, 1971

## ISOFLURANE AND CATECHOLAMINES

8. Östman M, Biber B, Martner J, Reiz S: Effects of isoflurane on vascular tone and circulatory autoregulation in the feline small intestine. *Acta Anaesthesiol Scand* 29:389-394, 1985
9. Takeshima R, Dohi S: Comparison of arterial baroreflex in humans anesthetized with enflurane or isoflurane. *Anesth Analg* 69:284-290, 1989
10. Kotrly KJ, Ebert TJ, Vucins E, Iglar FO, Barney JA, Kampine JP: Baroreceptor reflex control of heart rate during isoflurane anesthesia in humans. *ANESTHESIOLOGY* 60:173-179, 1984
11. Pavlin EG, Su JY: *Cardiopulmonary pharmacology, Anesthesia*. 3rd edition. Edited by Miller RD. New York, Churchill Livingstone, 1990, pp 105-134
12. Eger EI II: The pharmacology of isoflurane. *Br J Anaesth* 56:71S-99S, 1984
13. Black GW: Isoflurane in dental anaesthesia for children (letter). *Br J Anaesth* 59:522, 1987
14. Warde D, Nagi H, Raftery S: Respiratory complications and hypoxic episodes during inhalation induction with isoflurane in children. *Br J Anaesth* 66:327-330, 1991
15. Nishino T, Tanaka A, Ishikawa T, Hiraga K: Respiratory, laryngeal, and tracheal responses to nasal insufflation of volatile anesthetics in anesthetized humans. *ANESTHESIOLOGY* 75:441-444, 1991
16. Coleridge HM, Coleridge JCG, Luck JC, Norman J: The effect of four volatile anaesthetic agents on the impulse activity of two types of pulmonary receptor. *Br J Anaesth* 40:484-492, 1968
17. Ebert TJ, Kampine JP: Nitrous oxide augments sympathetic outflow: Direct evidence from human peroneal nerve endings. *Anesth Analg* 69:444-449, 1989
18. Naito H, Gillins CN: Effects of halothane and nitrous oxide on removal of norepinephrine from the pulmonary circulation. *ANESTHESIOLOGY* 39:575-580, 1973
19. Helman JD, Leung JM, Bellows WH, Pineda N, Roach GW, Reeves JD, Howse J, McEnany MT, Mangano DT, The SPI Research Group: The risk of myocardial ischemia in patients receiving desflurane *versus* sufentanil anesthesia for coronary artery bypass graft surgery. *ANESTHESIOLOGY* 77:47-62, 1992
20. Cullen DJ, Eger EI II: Cardiovascular effects of carbon dioxide in man. *ANESTHESIOLOGY* 41:345-349, 1974
21. Ornato JP, Garnett AR, Glauser FL: Relationship between cardiac output and the end-tidal carbon dioxide tension. *Ann Emerg Med* 19:1104-1106, 1990
22. Berne RM, Levy MN: *Control of cardiac output: Coupling of the heart and blood vessels, Principles of Physiology*. 1st edition. Edited by Berne RM, Levy MN. St Louis, Baltimore, CV Mosby, 1990, p 295
23. Ginn R, Vane JR: Disappearance of catecholamines from the circulation. *Nature* 219:740-742, 1968
24. Fishman AP, Pietra GG: Handling of bioactive materials by the lung (second of two parts). *N Engl J Med* 291:953-959, 1974
25. Derbyshire DR, Chmielewski A, Fell D, Vater M, Achola K, Smith G: Plasma catecholamine responses to tracheal intubation. *Br J Anaesth* 55:855-860, 1983