

Cardiovascular Safety and Actions of High Concentrations of I-653 and Isoflurane in Swine

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The ratio of lethal-to-anesthetic concentration can be used to define the margin of safety of an inhaled anesthetic. In mechanically ventilated swine the fatal concentration of I-653, a new inhaled anesthetic, was $23.9 \pm 0.06\%$ (mean \pm SE), and of isoflurane, $6.22 \pm 0.23\%$. The ratio of fatal anesthetic concentration-to-MAC for I-653 (2.45 ± 0.11) was less than that determined for isoflurane (3.02 ± 0.13 ; $P < 0.01$) but relatively greater than that reported previously for other inhaled anesthetics. As with other inhaled anesthetics, the concentration of I-653 causing cardiovascular collapse exceeds that producing apnea, making cardiovascular collapse during spontaneous ventilation unlikely. Mean aortic blood pressure and cardiac output decreased as linear functions of anesthetic concentration. Values for these variables for isoflurane were greater than those for I-653 at concentrations exceeding 1.5 MAC. Heart rate, blood lactate concentration, and base-deficit did not change with anesthetic depth. Mixed venous P_{O_2} , mixed venous oxyhemoglobin saturation, and the ratio of oxygen transport to oxygen consumption remained at or above values in conscious swine but decreased similarly with both anesthetics when anesthetic concentration increased to within 0.5 MAC of the fatal concentration. Thus, the latter three variables, reflecting the fraction of delivered oxygen that is consumed, and "mean" tissue P_{O_2} , appear to be useful indices of anesthetic concentrations approaching those producing cardiovascular collapse. (Key words: Anesthetic, volatile: I-653; isoflurane. Anesthetics, adverse effects: fatal concentration. Cardiovascular physiology, anesthetic effects: mixed venous oxyhemoglobin saturation; mixed venous P_{O_2} . Monitoring, cardiovascular.)

I-653 (difluoromethyl 1-fluoro, 2,2,2-trifluoroethyl ether) is a new inhaled anesthetic with cardiovascular^{1,2} and electroencephalographic³ effects similar to those of equipotent concentrations of isoflurane at 0.8 to 1.6 MAC in swine. In this study, we determined the margin of cardiovascular safety of I-653 relative to isoflurane by comparing the ratios of the concentration of each anesthetic

at cardiovascular collapse to their MAC. We also measured cardiovascular and metabolic effects of high concentrations of both anesthetics to identify physiologic changes indicative of the approach of dangerously high anesthetic concentrations.

Methods

This study was approved by the University of California, San Francisco Committee on Animal Research.

Indwelling aortic and 5-Fr thermodilution pulmonary arterial cannulae were inserted as previously described¹ in 11 young (age 11–15 wk; weight 20.7 ± 1.4 kg, mean \pm SE) female domestic swine. Five of these swine had been used earlier to study the cardiovascular effects of I-653 and isoflurane¹; five others had been used to study the interaction of succinylcholine, thiopental, fentanyl, atracurium, atropine, and edrophonium with I-653 or isoflurane; one animal had been used in both earlier studies. No anesthetics or drugs were administered for at least 2 days preceding this study. All animals were in good health, had normal core temperature, behaved normally, and displayed no effects of previously administered drugs or anesthetics.

Anesthesia was induced *via* a mask with I-653 ($n = 6$) or isoflurane ($n = 5$) in oxygen; anesthetics were randomly assigned. After induction of anesthesia, succinylcholine (2 mg/kg iv) was given to facilitate tracheal intubation. No other drugs were given. Body temperature was maintained within 0.5° C of the awake value by circulating-heated water pads. The animals' lungs were ventilated with tidal volumes of approximately 20 ml/kg, with frequency adjusted to maintain normocapnia.

Aortic, right atrial, and pulmonary arterial phasic and mean blood pressures, and pulmonary arterial wedge pressures were recorded on a polygraph (Gould Brush® 2800) from Statham® 23Db transducers. Cardiac output was determined by a thermodilution technique using an analog computer (Edwards 9520A), and injection of 3 ml of 0° C 0.9% NaCl into the right atrium during end-expiration. Cardiac output determinations were performed in duplicate. If the two measurements differed by more than 0.2 l/min, the determination was repeated. The mean of the two determinations differing by less than 0.2 l/min was taken as the correct value. Lead II of the ECG was recorded and pulmonary arterial temperature was measured throughout the experiment. Partial pres-

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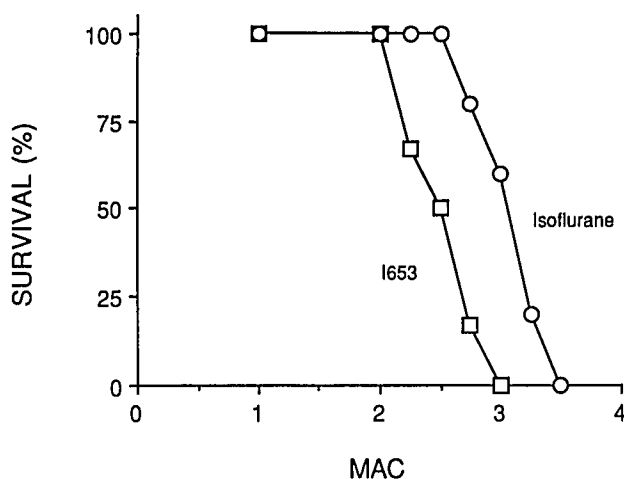


FIG. 1. Percent of swine surviving at increasing anesthetic concentration; decreases in parallel for I-653 (□; initial $n = 6$) and isoflurane (○; initial $n = 5$).

sure of carbon dioxide at the endotracheal tube orifice was measured by an infrared analyzer, Beckman® LB-2, Beckman Instruments, calibrated with a known concentration of CO_2 and recorded on a multichannel recorder (Gould Brush® 2800). End-tidal concentrations of anesthetics were measured by infrared analyzers (Beckman® LB-2, Beckman Instruments; and Puritan Bennett Anesthetic Agent Monitor 222) calibrated with secondary (tank) standards.

Aortic and pulmonary arterial (mixed venous) blood were sampled for measurement of pH and partial pressures of oxygen and carbon dioxide, and arterial blood was sampled for measurement of whole blood lactate concentration.⁵ Blood gas and pH values were corrected to the animal's temperature.^{6,7} Sampled blood was replaced with an equal volume of isotonic saline.

The initial anesthetic concentration given to each animal was 1.1–1.2 MAC. The MAC determined for each animal⁸ was used to determine the fatal-to-anesthetic ratio for each animal. Measurements were made after maintaining a stable end-tidal anesthetic concentration for 15 min. Anesthetic concentration was then increased by 0.35–0.4 MAC, and after 15 min of stable end-tidal concentration, measurements were repeated. This process

was repeated until the animal died, as indicated by lack of a pulsatile wave form transduced from the aortic and pulmonary arterial cannulae. If the animal did not survive for at least 10 min at the new (highest) anesthetic concentration, the previous (the next lower anesthetic concentration) concentration was considered to be fatal.

For each study state, we also calculated the following: oxygen content of arterial (CaO_2) and mixed venous (CvO_2) blood^{6,7} oxygen consumption, $\text{V}_{\text{O}_2} = 10 (\text{CaO}_2 - \text{CvO}_2)(\text{Q}_t)/\text{Wt}$, and oxygen transport, $\text{TO}_2 = 10 (\text{CaO}_2)(\text{Q}_t)/\text{Wt}$, where Q_t is cardiac output and Wt is body weight. Arterial blood base excess was determined from a nomogram for swine blood.⁹

For each anesthetic, data and computed values for each study state were compared using analysis of variance with repeated measures and the Newman-Keuls method of multiple comparisons.¹⁰ Data and computed values at approximately equipotent concentrations of I-653 and isoflurane were compared using Student's unpaired t test.¹⁰ The ratio of fatal anesthetic concentration-to-MAC for I-653 and isoflurane were compared using Student's unpaired t test.¹⁰ Statistical significance was accepted at $P \leq 0.05$.

Results

Survival of swine as a function of anesthetic concentration was closely parallel for I-653 and isoflurane, with a constant separation throughout of approximately $\frac{1}{2}$ MAC (fig. 1). MAC for I-653 ($n = 6$ swine) was $9.8 \pm 0.3\%$ (mean \pm SE), and the fatal concentration was $23.9 \pm 0.06\%$ (table 1), resulting in a fatal anesthetic concentration-to-MAC ratio of 2.45 ± 0.11 . MAC for isoflurane ($n = 5$) was $2.07 \pm 0.08\%$, and the fatal concentration was $6.22 \pm 0.23\%$, resulting in a fatal-to-anesthetic ratio of 3.02 ± 0.13 (table 1), which differed significantly from that for I-653 ($P < 0.01$).

The cardiovascular data obtained in these swine at 1.1–1.2 and 1.4–1.6 MAC agreed closely with previous data for these concentrations.¹ Increasing concentrations of I-653 and isoflurane progressively decreased mean aortic blood pressure and cardiac output ($P < 0.05$), but heart rate did not change significantly (fig. 2). Over the entire range of anesthetic concentrations we report in this study (which does not include values in conscious animals), cardiac output and blood pressure decreased as a linear function of anesthetic concentration (least squares linear regression):

$$\text{BP}_{\text{I-653}} = -35.7 \text{ MAC} + 106; \quad r^2 = 0.991$$

$$\text{BP}_{\text{isoflurane}} = -21.1 \text{ MAC} + 87; \quad r^2 = 0.972$$

$$\text{Q}_{\text{t-I-653}} = -94.0 \text{ MAC} + 269; \quad r^2 = 1.000$$

$$\text{Q}_{\text{t-isoflurane}} = -52.5 \text{ MAC} + 226; \quad r^2 = 0.941$$

TABLE 1. Fatal Concentrations of I-653 and Isoflurane in Swine

	MAC (%)	Fatal Concentration (%)	FAR
I-653	9.8 ± 0.3	23.9 ± 0.06	2.45 ± 0.11
Isoflurane	2.07 ± 0.08	6.22 ± 0.23	3.02 ± 0.13

Data are mean \pm SE. $N = 6$ for I-653, 5 for isoflurane.

FAR = ratio of fatal anesthetic concentration-to-MAC; significantly different between I-653 and isoflurane ($P < 0.01$).

At anesthetic concentrations greater than 1.4–1.6 MAC, mean aortic blood pressure and cardiac output were higher ($P < 0.05$) during isoflurane than during I-653 anesthesia, but heart rate did not differ. Blood lactate concentration and base deficit did not change with either anesthetic, even at very low levels of blood pressure and cardiac output.

Mixed venous oxyhemoglobin saturation ($S\bar{v}O_2$), mixed venous P_{O_2} ($P\bar{v}O_2$), and the ratio of oxygen transport to oxygen consumption (T_{O_2}/V_{O_2}) did not decrease to values below those in conscious swine in our earlier experiment¹ until the concentration of I-653 reached 2.0 MAC or isoflurane reached 2.4 MAC (fig. 3). At and above these higher anesthetic concentrations, values for these variables declined sharply ($P < 0.05$). In each animal, these decreases to less than conscious values heralded cardiovascular deterioration and death at the next higher anesthetic concentration. At the anesthetic concentrations causing cardiovascular collapse in each animal, and at the next lower concentration, the values for $P\bar{v}O_2$, $S\bar{v}O_2$, and T_{O_2}/V_{O_2} did not differ for I-653 and isoflurane (fig. 4).

Discussion

The mean fatal dose for I-653 was 2.45 ± 0.11 MAC and for isoflurane, 3.02 ± 0.13 MAC. These values place the margin of safety for I-653 between that for isoflurane and other halogenated anesthetics. Roberts *et al.*¹¹ found a ratio of fatal concentration to MAC of 3.43 ± 0.38 for isoflurane and 1.98 ± 0.06 for halothane in swine. Although that ratio for isoflurane appears to be greater than ours, their fatal concentration, $4.90 \pm 0.53\%$, is substantially less than our value, $6.22 \pm 0.23\%$. Their ratio appears greater because they used previously published MAC values for halothane¹² and isoflurane¹³ in swine, which we now believe to be too low.⁸ Correction of their data using the more recent and, we believe, more appropriate values for MAC in swine, decreases their resulting fatal-to-anesthetic ratio to 1.37 for halothane, which is 58% of the ratio of 2.37 for isoflurane. Our fatal-to-anesthetic ratio for I-653 was a higher fraction (81%) of the ratio for isoflurane than was the halothane fraction.¹¹ Similarly, Wolfson *et al.* found a greater ratio of fatal anesthetic concentration at cardiac failure to MAC for isoflurane (5.7) than for enflurane (3.3), methoxyflurane (3.7), and halothane (3.0).^{14,15} Thus, the latter three anesthetics have a lower fatal anesthetic concentration-to-

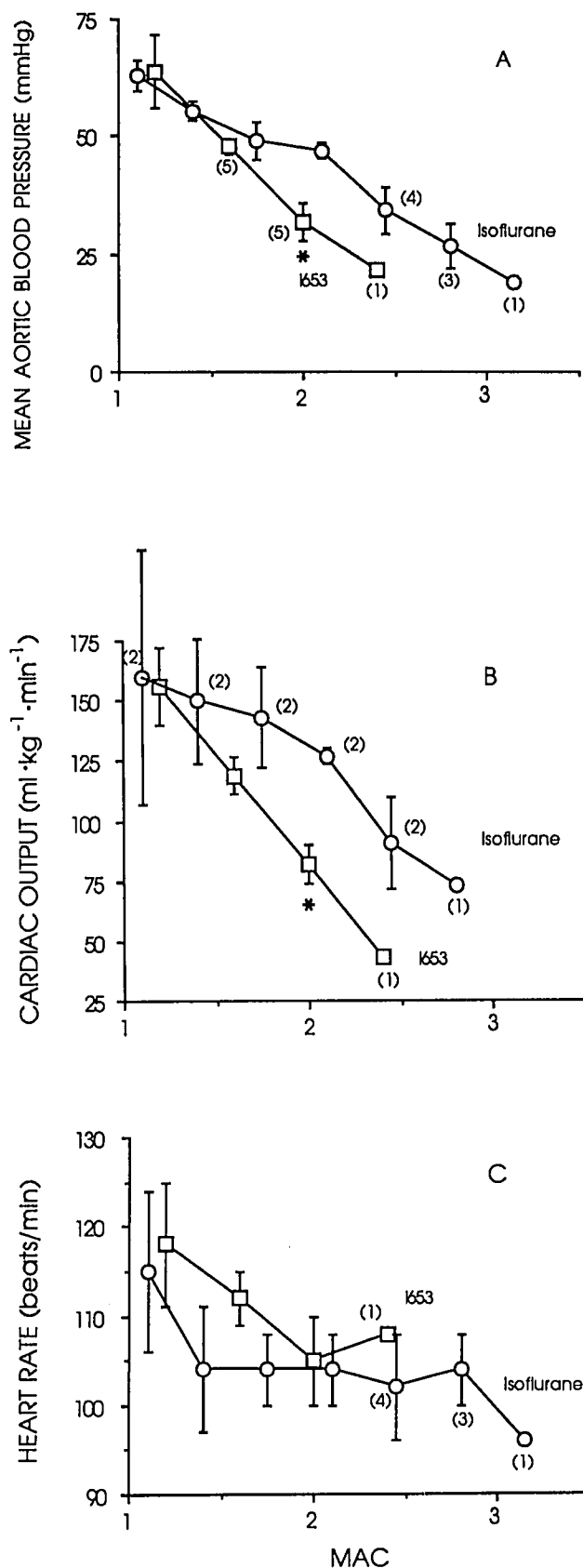


FIG. 2. Mean aortic blood pressure (A), and cardiac output (B) progressively decline, whereas heart rate (C) is unchanged with increasing concentrations of I-653 (□) or isoflurane (○). Data are mean \pm SE. For I-653 $n = 6$, and for isoflurane $n = 5$, unless otherwise indicated by a number in parentheses. *Values at equipotent concentrations of I-653 and isoflurane differ significantly ($P < 0.05$).

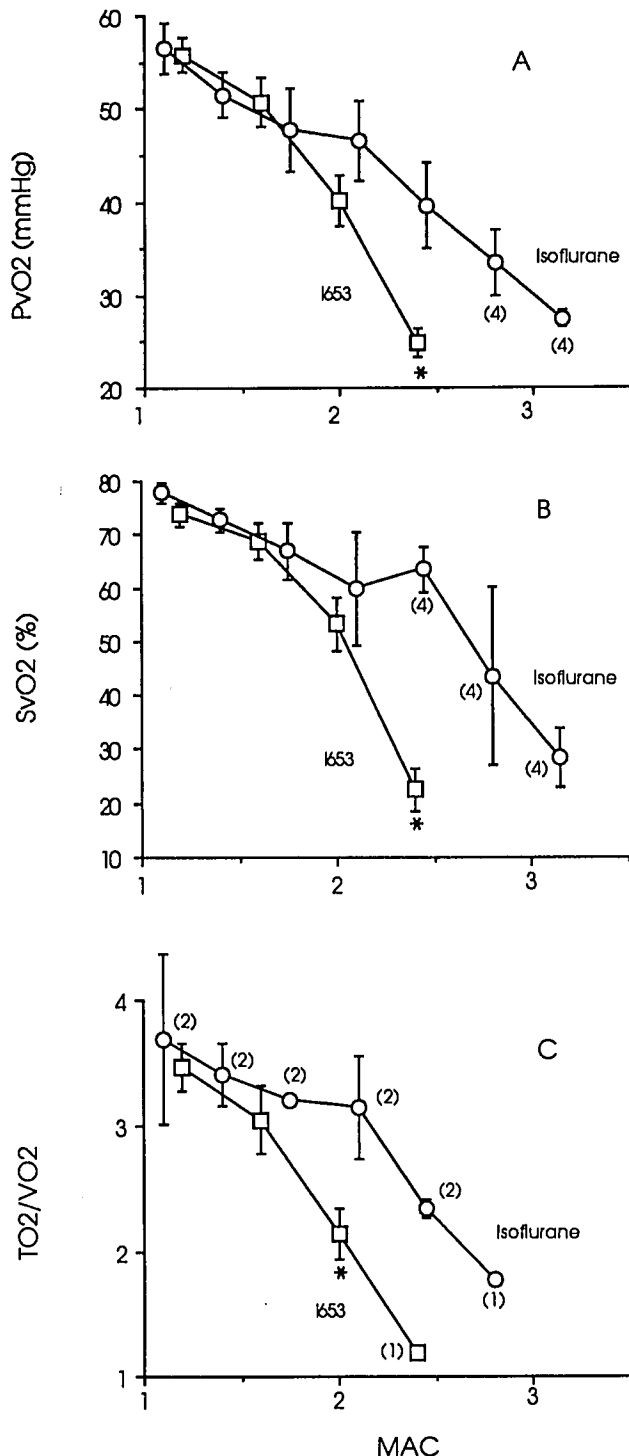


FIG. 3. Mixed venous P_{O_2} ($P\bar{V}_{O_2}$) (A), mixed venous oxyhemoglobin saturation ($S\bar{V}_{O_2}$) (B), and ratio of oxygen transport to consumption (T_{O_2}/V_{O_2}) (C) each decline precipitously as the concentrations of I-653 (□) or isoflurane (○) approach those producing cardiovascular collapse. Data are mean \pm SE. For I-653 $n = 6$, and for isoflurane $n = 5$, unless otherwise indicated by a number in parentheses. *Values at equipotent concentrations of I-653 and isoflurane differ significantly ($P < 0.05$).

MAC ratio (58%, 65%, and 53%) relative to isoflurane than that we found for I-653.

For each of these anesthetics, Wolfson *et al.*^{14,15} also noted that apnea occurred at substantially lower anesthetic concentrations than did cardiac failure, which confirmed the earlier findings of Regan and Eger¹⁶ who produced apnea without cardiovascular collapse during cyclopropane, diethyl ether, halothane, and methoxyflurane anesthesia in dogs. In our earlier studies, during which swine were allowed to breathe spontaneously at 0.7–0.8, 1.1–1.2, and 1.4–1.6 MAC I-653 and isoflurane, six of seven animals were apneic at 1.6 MAC I-653. Thus, I-653 offers an important clinical safety factor common to other inhaled anesthetics: with spontaneous ventilation, alveolar concentrations capable of causing cardiovascular collapse are not usually attainable because apnea (and consequently, the cessation of anesthetic uptake) occurs at a lower anesthetic concentration than does cardiovascular collapse. The concentration of I-653 causing cardiovascular collapse exceeds the concentration causing apnea by more than 50%.

However, inhaled anesthetics are frequently administered with controlled rather than spontaneous ventilation, thereby eliminating the critical safety factor provided by the latter. Guideposts that anticipate anesthetic depths bordering cardiovascular collapse might increase the safety of high concentrations administered with controlled ventilation. For example, the margin of safety for induction of deliberate hypotension with high concentrations of inhaled anesthetics might be increased if such guideposts were available. Surprisingly, few reports have described the cardiovascular effects of high concentrations of inhaled anesthetics. Newberg *et al.* examined the cerebral metabolic effects of isoflurane at concentrations up to 4 MAC but required infusions of fluid and phenylephrine to support blood pressure.¹⁷ Our data indicate that mean arterial blood pressure and cardiac output decrease as linear functions of increasing anesthetic concentration; thus, neither provides a readily recognizable danger point. Despite very low mean arterial blood pressures and cardiac outputs, our animals demonstrated surprising cardiovascular stability. Other potential indicators of excessive anesthetic concentration, heart rate, base deficit, and blood lactate concentration, also failed to mark perilously high concentrations of these anesthetics.

As anesthetic concentration in our study approached the fatal level, the variables that changed most noticeably were $P\bar{V}_{O_2}$, $S\bar{V}_{O_2}$, and T_{O_2}/V_{O_2} . In an individual animal, values for these variables fell to values less than those noted in conscious swine at anesthetic concentrations within 0.5 MAC of the fatal concentration. These variables reflect the fraction of delivered oxygen that is consumed, and the resultant "mean total-body" tissue P_{O_2} .

In a notable series of experiments spanning three de-

cares, Cain *et al.* showed that oxygen consumption fell and lactate began to accumulate when acute anemia or acute hypoxia decreased oxygen transport below a "critical value" of $10\text{--}12 \text{ ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in barbiturate-anesthetized dogs,^{18,19} and at twice that value in similarly anesthetized rats.²⁰ Because oxygen consumption decreases with increasing anesthetic depth, oxygen transport cannot be used to assess inadequate tissue oxygenation in the presence of changing anesthetic concentration. The critical value for oxygen transport for swine or humans is not known. In our swine $\bar{P}\bar{V}\text{O}_2$, $\bar{S}\bar{V}\text{O}_2$, and TO_2/VO_2 did not decrease below the value for the awake state until TO_2 fell to $10.6 \pm 0.8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, a value similar to the "critical" value found by Cain in dogs. With changing anesthetic depth and thus oxygen consumption, the ratio of oxygen transport to consumption appears to be a better indicator of the limit of adequate tissue oxygenation and, by implication, adequate oxygen delivery than are other cardiovascular parameters. Although we decreased oxygen transport by decreasing cardiac output, rather than by producing hypoxemia as did Cain, we achieved somewhat similar results: our swine did not display detrimental effects of high anesthetic concentration until $\bar{S}\bar{V}\text{O}_2$ decreased to less than 50%. Similarly, in dogs made acutely hypoxemic or with an acutely imposed mechanical decrease in hepatic blood flow, Tashkin *et al.* found that hepatic venous lactate did not increase until hepatic venous oxyhemoglobin saturation fell below 50%.²¹

Acute changes in blood lactate concentration and base deficit reflect a balance of total-body lactate production and the liver's ability to extract and metabolize lactate,²² a function that is impaired during hepatic hypoperfusion or hypoxia.²¹ We saw no increase in arterial blood lactate concentration despite decreases in cardiac output exceeding 50%. During normoxia hepatic venous lactate does not increase until hepatic blood flow is decreased by more than 70%.²¹ Infusions of lactate or increases in lactate production increase arterial lactate concentration with a half-time of approximately 20–60 min, although hepatic extraction and metabolism also increase.²² Thus, apparently our swine did not have increased lactate production, nor markedly decreased hepatic blood flow, at least until the two highest anesthetic concentrations were reached, when there may have been insufficient time to produce measurably increased blood lactate concentration, had either condition occurred.

It is possible that the results of this study performed in "adolescent" swine might not be directly applicable to adult humans. However, the cardiovascular system of swine is similar to that of humans²³ and has reached maturity by the age of the animals we used.²⁴

In summary, the margin of cardiovascular safety of I-653 is greater than that for enflurane, halothane, and methoxyflurane, but not as great as that for isoflurane.

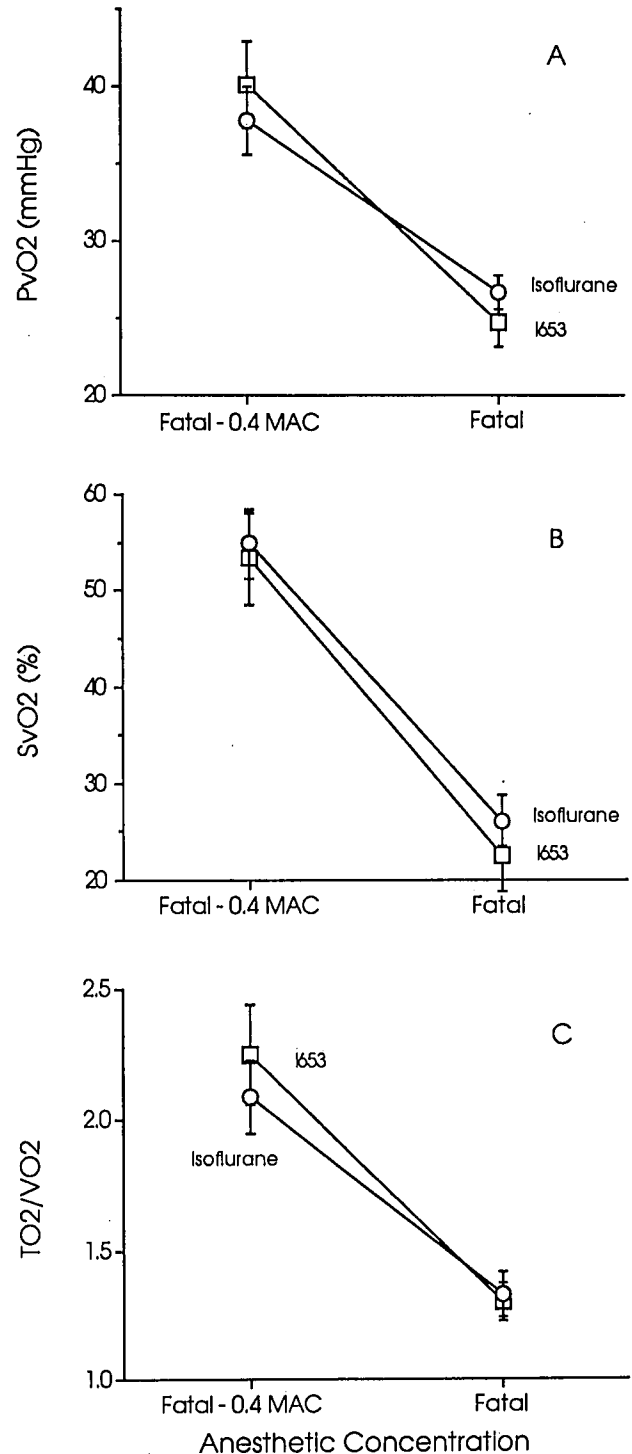


FIG. 4. Mixed venous PO_2 (A), mixed venous oxyhemoglobin saturation ($\bar{S}\bar{V}\text{O}_2$) (B), and the ratio of oxygen transport to oxygen consumption (TO_2/VO_2) (C) at the fatal and next lower anesthetic concentration do not differ between I-653 (□; $n = 6$) and isoflurane (○; $n = 5$). Note that the abscissa values are normalized individually for each pig to the concentration producing cardiovascular collapse (fatal). Data are mean \pm SE. There were no significant differences between values at equipotent concentrations of I-653 and isoflurane.

The best indices of excessive anesthetic concentration were mixed venous P_{O_2} , mixed venous oxyhemoglobin saturation, and the ratio of oxygen transport-to-oxygen consumption. Values for these variables fell below those in conscious swine only when concentrations of I-653 or isoflurane increased to within 0.5 MAC of the concentration causing cardiovascular collapse.

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