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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 ± 0.06% (mean ± SE), and of isoflurane, 6.22 ± 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 electroencephalographic[3] 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.

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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 described[1] in 11 young (age 11–15 wk; weight 20.7 ± 1.4 kg, mean ± SE) female domestic swine. Five of these swine had been used earlier to study the cardiovascular effects of I-653 and isoflurane[1]; 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-