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Cardiovascular Effects of I653 in Swine

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I653 (difluoromethyl 1-fluoro 2,2,2-trifluoroethyl ether) is a new inhalation anesthetic with a low blood-gas partition coefficient and no demonstrable toxicity. The authors examined its cardiovascular effects at 0.8, 1.2, and 1.6 MAC in eight chronically instrumented domestic swine mechanically ventilated to maintain normocarbia. These data were compared with those obtained while the animals were conscious and while anesthetized with isoflurane at approximately equal MAC multiples. I653 caused dose-related decreases in mean arterial blood pressure (95 ± 2 mmHg, mean ± SE, conscious; 65 ± 3 mmHg, 0.8 MAC; 55 ± 3 mmHg, 1.2 MAC; and 48 ± 2 mmHg, 1.6 MAC). At 0.8 MAC, systemic vascular resistance decreased 35% from the conscious condition value. Despite the decreases in blood pressure and systemic vascular resistance, and dose-dependent increases in right- and left-heart filling pressures, stroke volume fell in a dose-related fashion (2.11 ± 0.10, 1.57 ± 0.08, 1.37 ± 0.06, and 1.10 ± 0.06 ml/kg; conscious, 0.8, 1.2, and 1.6 MAC). At 0.8 MAC, cardiac output was unchanged (220 ± 12 $ml \cdot min^{-1} \cdot kg^{-1}$) from the conscious condition (210 ± 8 $ml \cdot min^{-1} \cdot kg^{-1}$), as heart rate increased (142 ± 7 beats/min, at 0.8 MAC *vs.* 100 ± 3 beats/min, conscious) and systemic vascular resistance decreased. At concentrations greater than 0.8 MAC, heart rate decreased towards but did not reach the conscious value (127 ± 4 at 1.2 MAC, 120 ± 4 at 1.6 MAC). Systemic vascular resistance increased slightly at 1.6 MAC compared to the values at 0.8 and 1.2 MAC, but was always less than in the conscious condition. I653 concentrations exceeding 0.8 MAC decreased cardiac output (174 ± 10 $ml \cdot min^{-1} \cdot kg^{-1}$ at 1.2 MAC and 133 ± 10 $ml \cdot min^{-1} \cdot kg^{-1}$ at 1.6 MAC) despite the increased pre-load. I653 also caused dose-dependent decreases in oxygen consumption and left ventricular minute work. No detrimental effect of this depression was found: the ratio of oxygen transport to oxygen consumption and mixed venous oxyhemoglobin saturation were increased slightly or unchanged from the conscious value; base-excess increased with anesthesia and did not change with anesthetic concentration; and blood lactate concentration did not change. Neither pulmonary vascular resistance nor pulmonary arterial pressure changed at any concentration of I653. The cardiovascular actions of I653 were not distinguishable from those of isoflurane. The authors conclude that I653 has safe cardiovascular effects in normal domestic swine, at clinically useful anesthetic concentrations. (Key words: Anesthetics, volatile: I653; isoflurane. Blood lactate. Cardiovascular physiology: anesthetic effects.)

I653 (DIFLUOROMETHYL 1-FLUORO 2,2,2-TRIFLUOROETHYL ETHER) is a new inhalation anesthetic with several advantageous biophysical properties. Its blood/gas partition coefficient of 0.42,[1] lower than that of other halogenated anesthetics and of nitrous oxide,[2] predictably results in a more rapid induction of and emergence from anesthesia in laboratory animals than achieved with other potent inhaled anesthetics.[3] I653 is stable in soda lime[4] and is not flammable. Studies performed thus far have demonstrated little or no metabolism of I653[5] and no toxicity.[6] These desirable properties prompted us to pursue studies with I653, to define further its pharmacologic properties. This report describes the cardiovascular actions of I653 at three anesthetic concentrations, in chronically instrumented domestic swine, and compares these actions with those of approximately equipotent concentrations of isoflurane, as well as with data obtained when the animals were conscious.

Materials and Methods

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

CHRONIC INSTRUMENTATION

Eight domestic female swine (weight: 17.0 ± 2.4 kg, mean ± SE; age approximately 12 weeks) were anesthetized with halothane. Through a left flank incision, the aorta was exposed by retroperitoneal dissection. A large bore (3 mm internal diameter) cannula was inserted into the infrarenal aorta and tunnelled subcutaneously to the mid-dorsum where, for protection, the cannula exited into a Keyloc® pouch. A 5-French pulmonary arterial cannula was inserted percutaneously through the suprasternal area into the innominate vein and advanced into the pulmonary artery, as judged by recorded intravascular pressures and the ability to obtain a "wedge" pressure with the balloon inflated. The pulmonary arterial cannula was then positioned with the proximal port in the right atrium. The pulmonary arterial cannula was also tunnelled subcutaneously to the mid-dorsum where it exited into a Keyloc® pouch separate from that protecting the aortic cannula. To prevent clotting, all cannula lumena were filled (or refilled

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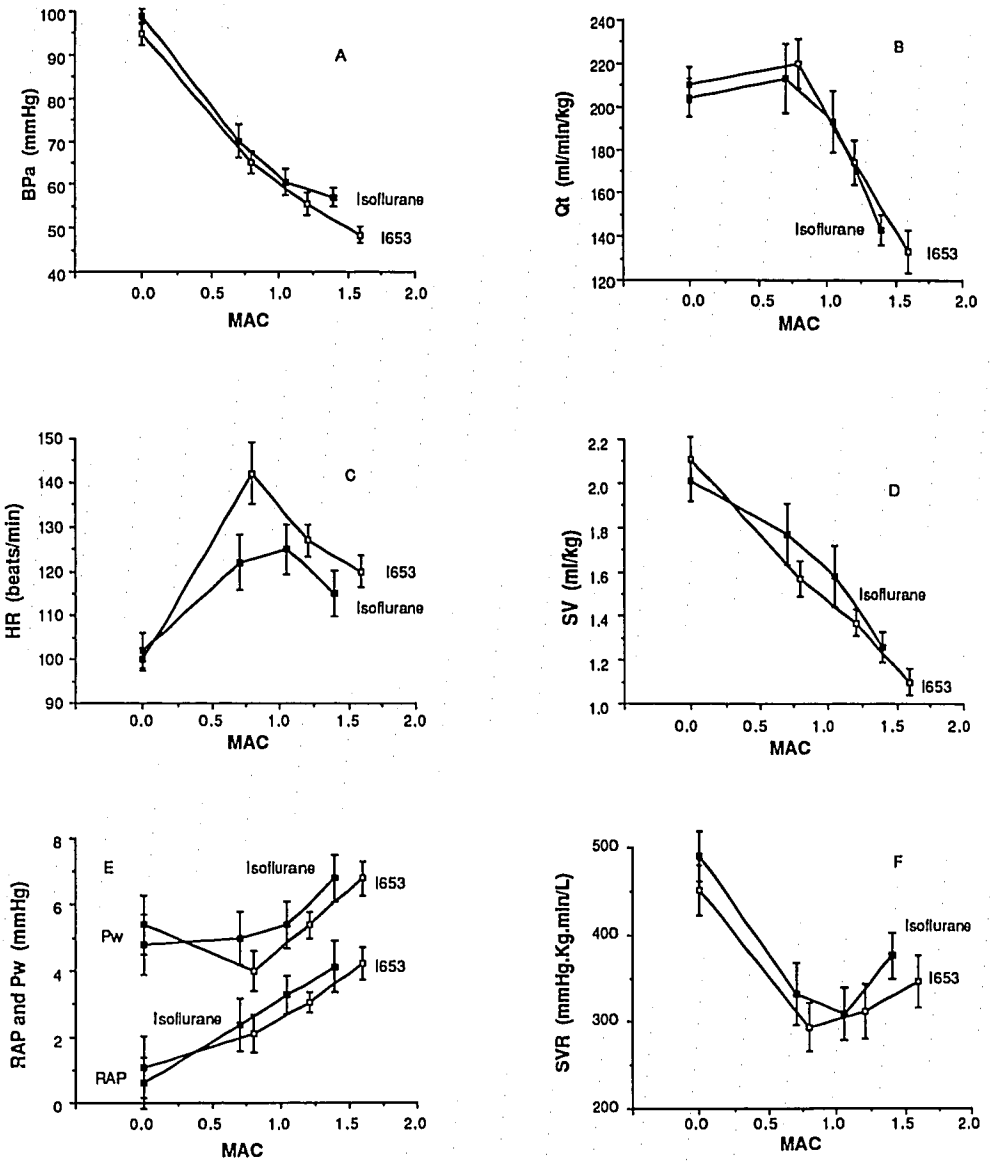

FIG. 1. *A.* Mean aortic blood pressure (BPa); *B.* cardiac output (Q_t); *C.* heart rate (HR); *D.* stroke volume (SV); *E.* right atrial (RAP) and pulmonary arterial "wedge" (Pw) pressures; and *F.* systemic vascular resistance (SVR); in eight swine, conscious and anesthetized with I653 (□) or isoflurane (■). See table 2 for statistical significance.

after aspiration) with heparin (10,000 units/ml) every 2–3 days. Animals were given cefazolin for 3 days following surgery.

DETERMINATION OF CARDIOVASCULAR EFFECTS

Prior to and after surgery, animals were accustomed to the laboratory personnel and the laboratory environment, including a padded swine sling[7] (Charles River Laboratories). The sling supported the animal's ventral surface and allowed the legs to extend, unsupported, toward the ground. Three to seven days after surgery, with the animals in good health, each conscious pig was placed in the sling. Cardiovascular measurements were made after at least 10 min of stable arterial blood pressure and heart rate. When these measurements were performed, some animals appeared to be asleep (indicated by closed eyes and respiratory pattern); all rested calmly. Aortic, right atrial, and pulmonary arterial phasic and mean blood pressures, and pulmonary arterial "wedge" pressure were recorded on a polygraph (Gould Brush® 2800) from Statham® 23Db pressure transducers. Cardiac output was determined by 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 similar determinations was taken as the correct value. Lead II of the electrocardiogram was recorded and pulmonary arterial temperature was measured throughout

TABLE 1. Hemodynamic and Metabolic Data*

Variable	I653				Isoflurane			
	Conscious	0.8 MAC	1.2 MAC	1.6 MAC	Conscious	0.7 MAC	1.05 MAC	1.4 MAC
T, ° C	38.9 ± 0.2	38.8 ± 0.1	38.9 ± 0.1	38.9 ± 0.1	38.9 ± 0.2	38.7 ± 0.2	38.8 ± 0.1	38.9 ± 0.1
Pa_{O_2}, mmHg†	104 ± 5	375 ± 8	351 ± 9	334 ± 13	93 ± 3	413 ± 20	407 ± 19	393 ± 21
Pa_{CO_2}, mmHg	43.1 ± 1.5	42.7 ± 1.2	42.4 ± 1.1	44.6 ± 1.0	44.6 ± 1.0	43.7 ± 1.4	45.3 ± 1.4	46.6 ± 1.3
pHa, units	7.458 ± 0.004	7.506 ± 0.009	7.509 ± 0.010	7.485 ± 0.010	7.460 ± 0.004	7.501 ± 0.010	7.483 ± 0.009	7.472 ± 0.007
Anes conc, %	0 ± 0	7.82 ± 0.07	11.66 ± 0.15	15.58 ± 0.16	0 ± 0	1.42 ± 0.01	2.11 ± 0.02	2.80 ± 0.01
BPa, mmHg	95 ± 2	65 ± 3	55 ± 3	48 ± 2	99 ± 2	70 ± 4	60 ± 3	57 ± 2
Q_t, ml·min^{-1}·kg^{-1}	210 ± 8	220 ± 12	174 ± 10	133 ± 10	204 ± 9	214 ± 16	193 ± 14	143 ± 7
HR, beats/min	100 ± 3	142 ± 7	127 ± 4	120 ± 4	102 ± 4	122 ± 6	125 ± 7	115 ± 5
RAP, mmHg	1.1 ± 0.9	2.1 ± 0.6	3.0 ± 0.3	4.2 ± 0.5	0.6 ± 0.8	2.4 ± 0.8	3.3 ± 0.6	4.1 ± 0.8
Pw, mmHg	5.4 ± 0.9	4.0 ± 0.6	5.4 ± 0.4	6.8 ± 0.5	4.8 ± 0.9	5.0 ± 0.8	5.4 ± 0.7	6.8 ± 0.7
SV, ml/kg	2.11 ± 0.10	1.57 ± 0.08	1.37 ± 0.06	1.10 ± 0.06	2.02 ± 0.09	1.77 ± 0.14	1.58 ± 0.14	1.26 ± 0.07
SVR, mmHg·kg·min/l	451 ± 29	294 ± 28	312 ± 31	346 ± 30	490 ± 29	332 ± 36	309 ± 31	376 ± 27
PAP, mmHg	14.9 ± 0.8	12.8 ± 0.6	12.4 ± 0.5	13.1 ± 0.7	12.9 ± 0.8	13.6 ± 0.7	13.7 ± 0.9	13.5 ± 0.8
PVR, mmHg·kg·min/l	45.9 ± 3.7	40.2 ± 2.2	40.8 ± 1.6	47.9 ± 2.3	39.9 ± 3.6	40.7 ± 2.4	43.3 ± 3.0	46.2 ± 1.7
LVMW, mmHg·g/min	461 ± 21	327 ± 22	225 ± 13	152 ± 13	460 ± 35	351 ± 22	280 ± 18	196 ± 12
VO_2, mlO_2·min^{-1}·kg^{-1}	8.06 ± 0.34	7.03 ± 0.43	6.43 ± 0.25	5.58 ± 0.57	8.08 ± 0.62	6.71 ± 0.40	6.67 ± 0.27	5.20 ± 0.36
TO_2/VO_2	3.19 ± 0.06	4.18 ± 0.33	3.46 ± 0.23	3.40 ± 0.64	3.09 ± 0.22	4.03 ± 0.12	3.64 ± 0.13	3.57 ± 0.34
S_vO_2, %	69.6 ± 0.8	80.6 ± 2.3	75.1 ± 2.5	70.7 ± 3.8	66.6 ± 3.4	81.6 ± 1.0	78.1 ± 1.4	76.6 ± 2.7
Blood lactate, mmol/l	1.17 ± 0.25	1.09 ± 0.06	1.02 ± 0.09	1.20 ± 0.15	1.28 ± 0.25	0.80 ± 0.11	0.81 ± 0.10	1.01 ± 0.17
BE, meq/l	5.6 ± 0.9	9.0 ± 0.6	9.1 ± 1.0	8.5 ± 0.8	6.5 ± 0.3	9.3 ± 1.1	8.6 ± 0.9	8.4 ± 0.7

T = pulmonary arterial blood temperature; Pa_{O_2} = arterial blood partial pressure of oxygen; Pa_{CO_2} = arterial blood partial pressure of carbon dioxide; Anes Conc = anesthetic concentration; BPa =mean aortic blood pressure; Q_t = cardiac output; HR = heart rate; RAP = right atrial pressure; Pw = pulmonary arterial "wedge" pressure; SV = stroke volume; SVR = systemic vascular resistance; PAP = mean pulmonary arterial blood pressure; PVR = pulmonary vascular resistance; LVMW = left ventricular minute work; VO_2 = oxygen consumption; TO_2/VO_2 = oxygen transport/oxygen consumption; S_vO_2 = mixed venous oxyhemoglobin saturation; BE = base-excess. Data are mean ± SE. N = 8.

* See table 2 for statistical interpretation of data.

† Fi_{O_2} in conscious state = 0.21; when anesthetized = approximately 0.7.

the experiment. Aortic and pulmonary arterial (mixed venous) blood were sampled for measurement of *p*H, and partial pressures of oxygen and carbon dioxide, and arterial blood was sampled for measurement of whole blood lactate concentration.[8] Blood gas and *p*H values were corrected to the animal's temperature.[9,10] Sampled blood was replaced with an equal volume of isotonic saline.

Following measurements in the conscious state, animals were anesthetized with either I653 or isoflurane at three randomized, approximately equipotent concentrations. The choice of anesthetic was randomized. Three to eight days later, measurements in the conscious state were repeated in each animal, and the alternate anesthetic administered. Anesthesia was induced by administering the anesthetic in oxygen *via* a mask. When the animal was asleep, succinylcholine, 2 mg/kg, was injected through the right atrial lumen of the pulmonary arterial cannula, to facilitate tracheal intubation. No other drugs were given. A closed circle absorption system was used for maintenance of anesthesia. Animals were placed in the left lateral decubitus position and their lungs were mechanically ventilated with a tidal volume of approximately 20 ml/kg; ventilatory frequency was adjusted to maintain normocarbia throughout the experiment. Pulmonary arterial temperature was maintained within 0.5° C of the conscious state value by the use of circulating heated water pads, as necessary. All measurements were repeated after 15 min of stable end-tidal anesthetic concentrations, in random order, equivalent to approximately 0.75, 1.13, and 1.5 MAC, as measured by infra-red analyzers (Beckman® LB-2, Beckman Instruments; and Puritan-Bennett® Anesthetic Agent Monitor 222). Each instrument was calibrated with known concentrations of anesthetic.

DETERMINATION OF MAC

We determined MAC for I653 in these swine.[11] Since we could not predict what the MAC for I653 for the entire group would be, we used the mean of the determinations in the first two animals, 7.9%, for this

TABLE 2. Statistical Interpretation

Variable	I653	Isoflurane
T	N	N
Pa_{O_2}	BCD > A	BCD > A
Pa_{CO_2}	N	N
*p*Ha	BC > D > A	BCDA
BPa	A > B > C > D	A > B > CD
Qt	BA > C > D	BAC > D
HR	B > CD > A	CBD > A
RAP	DCBA	DCB > A
Pw	DACB	DCBA
SV	A > B > C > D	A > B > C > D
SVR	A > DCB	A > D > BC
PAP	N	N
PVR	N	N
LVMW	A > B > C > D	A > B > C > D
VO_2	A > BCD	A > BC > D
TO_2/VO_2	BCDA	N
S_vO_2	BCDA	BCD > A
Blood Lactate	N	N
BE	CBD > A	BCDA

For abbreviations of variables and units, see table 1. N = not statistically significant; S = $P < 0.05$ (multiple analysis of variance with repeated measures and Newman-Keuls method of multiple comparisons). Abbreviations for stats: A = conscious; B = 0.7 MAC isoflurane, 0.8 MAC I653; C = 1.05 MAC isoflurane, 1.2 MAC I653; D = 1.4 MAC isoflurane, 1.6 MAC I653. Groups are ordered in decreasing magnitude, left to right; values not different from one another are joined by an underline. No value for any variable at any concentration of I653 was statistically different from the value at the equipotent concentration of isoflurane except for Pa_{O_2}, which was different at all anesthetic concentrations except 0.0.

study. Subsequently, we found the MAC of I653 for the entire group of eight animals was somewhat greater (10.0 ± 0.5%). For the MAC of isoflurane, we used the published value of 1.45%.[12,13] However, determination of isoflurane MAC in the last four animals of our group revealed that it, too, was greater (2.04 ± 0.11%). Consequently, our experiments were conducted at 0.8, 1.2, and 1.6 MAC for I653, and 0.7, 1.05, and 1.4 MAC for isoflurane, rather than the intended 1.0, 1.5, and 2.0 MAC for both anesthetics.

For each study condition, conscious and three levels of anesthesia, we also computed the following: stroke volume, SV = Q_t/HR; systemic vascular resistance, SVR = (BPa − RAP) (Wt)/Q_t; pulmonary vascular resistance, PVR = (PAP − Pw) (Wt)/Q_t; oxygen content of arterial (CaO_2) and mixed venous (CvO_2) blood;[9,10] oxygen consumption, Vo_2 = 10(CaO_2 − CvO_2) (Q_t)/Wt; oxygen transport, To_2 = 10(CaO_2) (Q_t)/Wt; and left ventricular minute work, LVMW = (BPas) (Q_t) (1.057); where BPa is mean aortic blood pressure, BPas is systolic blood pressure, Q_t is cardiac output, RAP is right atrial pressure, PAP is mean pulmonary arterial pressure, Pw is pulmonary artery "wedge" pressure, and Wt is body weight. Arterial blood base-excess was determined from a nomogram for swine blood.[14]

STATISTICAL ANALYSES

For each anesthetic, data and computed values for each of the four study states (conscious state and three anesthetic levels) were compared using analysis of variance with repeated measures and the Newman-Keuls method of multiple comparisons.[15] Data and computed values at approximately equipotent concentrations of I653 and isoflurane also were compared using analysis of variance with repeated measures and the Newman-Keuls method of multiple comparisons.[15] Statistical significance was accepted at $P < 0.05$.

Results

I653 caused dose-dependent decreases in mean aortic blood pressure (fig. 1A, tables 1 and 2, all values significantly different from one another) and stroke volume (fig. 1D; all values significantly different from one another). Stroke volume decreased despite a dose-dependent increase in right atrial pressure (fig. 1E; all values significantly different from one another), a dose-dependent increase in pulmonary arterial "wedge" pressure during anesthesia (fig. 1E), and a decrease in systemic vascular resistance from the conscious state at all concentrations of I653 (fig. 1F). Systemic vascular resistance at 1.2 MAC was not different from that at 0.8 MAC, but was slightly less than that at 1.6 MAC. At 0.8 MAC, heart rate increased above that during the conscious state (fig. 1C), while cardiac output remained unchanged (fig. 1B). With increasing concentrations of I653, cardiac output decreased in a dose-dependent fashion, despite increases in right- and left-heart preload (all values significantly different from each other). Heart rate decreased at 1.2 MAC and 1.6 MAC in comparison to 0.8 MAC. These values for heart rate did not differ from each other, but were greater than the heart rate during the conscious state.

I653 caused dose-dependent decreases in oxygen consumption (all values different from each other; fig. 2B) and left ventricular minute work (all values different from each other; fig. 2A) from the conscious state through all levels of anesthesia. The ratio of oxygen transport to oxygen consumption increased 31% at 0.8 MAC, and mixed venous oxyhemoglobin saturation increased at 0.8 MAC, but at 1.2 and 1.6 MAC these values did not differ from each other or from the values at 0.8 MAC or the conscious state (fig. 2C). Base-excess

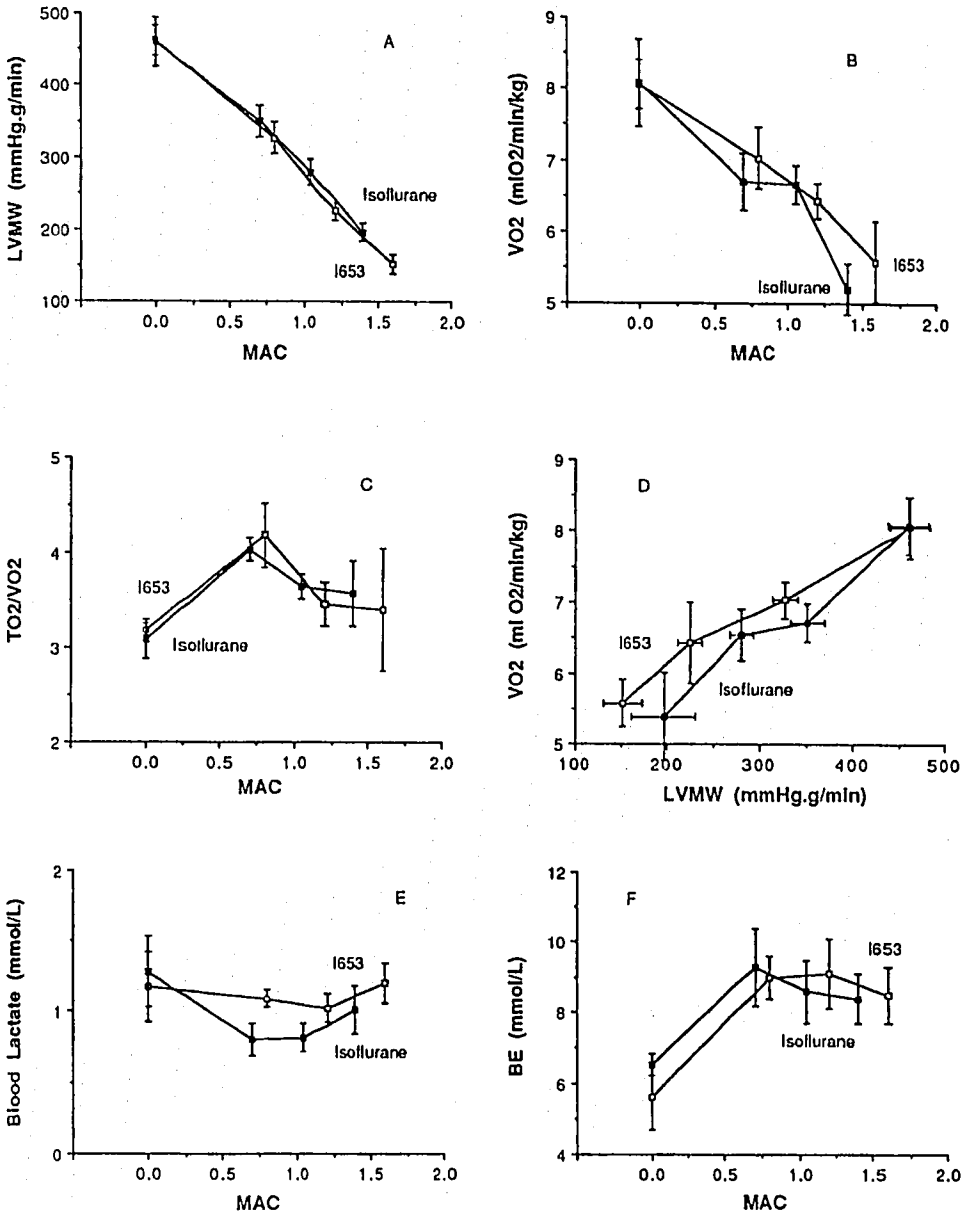

FIG. 2. *A.* Left ventricular minute work (LVMW); *B.* total body oxygen consumption (VO_2); *C.* ratio of oxygen transport to oxygen consumption (TO_2/VO_2); *D.* relationship of VO_2 and LVMW; *E.* blood lactate concentration; and *F.* base-excess (BE); in eight swine, conscious and anesthetized with I653 (□) or isoflurane (■). See table 2 for statistical significance.

increased with I653 anesthesia, but did not vary with I653 concentration (fig. 2F). No changes occurred in blood lactate concentrations at any concentration of I653 (fig. 2E).

I653 had no effect on the pulmonary circulation; neither pulmonary vascular resistance (fig. 3B) nor pulmonary artery pressure (fig. 3A) changed at any concentration of I653.

The changes observed with isoflurane anesthesia were indistinguishable from those observed with I653. There were no differences for any variable in the conscious state on the two separate study days, or between I653 and isoflurane at any of the three approximately equipotent concentrations of anesthetic studied.

Discussion

I653, in swine, has potent cardiovascular depressant properties similar to those of isoflurane. I653 is a vasodilator, substantially decreasing systemic vascular resistance and mean arterial blood pressure at all concentrations studied. Although this study was not designed to assess directly myocardial contractility, our results strongly suggest that I653 is a myocardial depressant. Increasing concentrations of I653 decreased stroke volume substantially despite increases in pre-load (right atrial and pulmonary arterial "wedge" pressures; fig. 4), albeit accompanied by small changes in heart rate, and after-load (systemic vascular resistance). The rela-

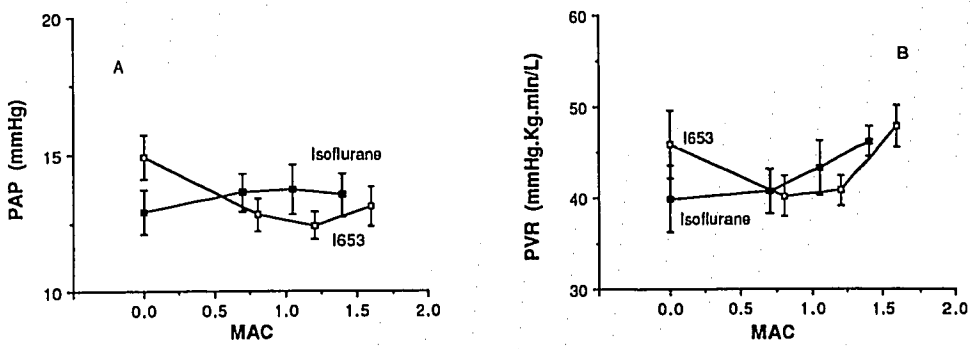

FIG. 3. *A.* Mean pulmonary arterial blood pressure (PAP); and *B.* pulmonary vascular resistance (PVR); in eight swine, conscious, and anesthetized with I653 (□) or isoflurane (■). See table 2 for statistical significance.

tionship between stroke volume (or cardiac output) and pre-load for I653 was identical to that for isoflurane, indicating a depression of myocardial contractility similar to that of isoflurane.

Despite substantial reductions in stroke volume, cardiac output, and mean aortic blood pressure, our limited testing did not detect detrimental systemic effects of I653. Left ventricular minute work and total body oxygen consumption decreased in parallel with increasing concentrations of I653 (fig. 2D). Base-deficit and blood lactate concentrations did not increase with anesthesia. Furthermore, all animals were standing and eating 7.5 ± 0.7 min after termination of administration of I653, and appeared completely normal in all respects during the subsequent several days to 2 weeks.

Our results in swine may differ from the cardiovascular effects of I653 in humans. Although the cardiovascular system of swine is similar to that of humans, anesthetic requirement for intravenous[16] and inhaled[12,13,17] anesthetics is greater in swine than in humans. If the cardiovascular actions of I653 are more closely related to the concentration of I653 than to the MAC of I653, equivalent multiples of MAC for I653 may be less depressant in humans than in swine. This hypothesis is supported by our data for isoflurane. In swine, we found that isoflurane caused cardiovascular depression similar to that of equivalent multiples of MAC of I653. In humans, Stevens *et al.*[18] found no change in cardiac output, and smaller increases in right atrial pressure at 1.2, 1.8, and 2.4% isoflurane (approximately 1, 1.5, and 2 MAC) than we observed at those MAC equivalents in swine. Mean arterial blood pressure fell less in humans than in our swine on a "per MAC" basis, but by an equivalent amount in terms of absolute concentration (approximately 20% decrease in blood pressure with each percent increase in absolute isoflurane concentration).

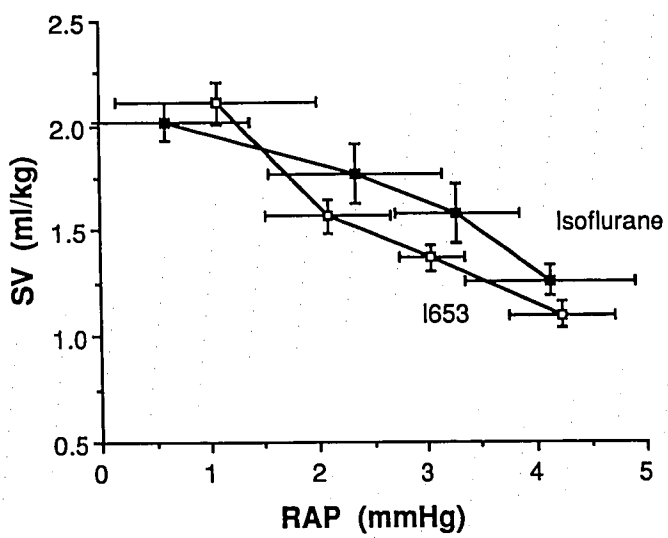

FIG. 4. Relationship of stroke volume (SV) and right atrial pressure (RAP) in eight swine, conscious and anesthetized with I653 (□) or isoflurane (■). There were no differences between I653 and isoflurane for SV at any RAP. Lines connecting data points do not imply that this fgure represents a single continuous "Frank-Starling" curve, but rather connects single points from a family of such curves.

Lundeen *et al.*[12] examined the cardiovascular effects of isoflurane in swine and found decreases in mean arterial blood pressure similar to those we observed at 1.4% and 2.1% isoflurane. Their swine exhibited no changes in heart rate, left atrial blood pressure, or systemic vascular resistance when anesthetized, compared to the conscious values, but their conscious swine had greater heart rate, mean arterial blood pressure, cardiac output, and left atrial blood pressure values than did our animals. Possibly the mask placed over the snouts of their conscious animals, to deliver oxygen and maintain hyperoxia, stimulated the swine, altered the "resting" values, and confounded the comparison with anesthetized values.

Both I653 and isoflurane cause hypotension and increased heart rate. Each of these effects is potentially undesirable. Both anesthetics also cause peripheral vasodilation. We did not measure coronary artery blood flow; however, it is possible that, like isoflurane,[19,20] I653 may cause coronary artery vasodilation and, in the presence of coronary artery stenosis, may cause coronary "steal" and regional myocardial dysfunction.

In summary, I653 has cardiovascular actions similar

to isoflurane in swine, causing vasodilation, hypotension, and dose-dependent myocardial depression. Ours and other studies suggest that I653 will have cardiovascular actions in humans similar to those of isoflurane, but less severe than those we observed in swine. However, even at the highest I653 concentrations, we did not detect increased anaerobic metabolism. Thus, I653 appears to have safe cardiovascular actions at clinically useful concentrations.

References

1. Eger EI II: Partition coefficients of I-653 in human blood, saline, and olive oil. Anesth Analg 66:971–973, 1987
2. Eger EI II: Uptake of inhaled anesthetics: The alveolar to expired anesthetic difference, Anesthetic Uptake and Action. Baltimore, Williams and Wilkins, 1974, pp 77–96
3. Eger EI II, Johnson BH: Rates of awakening from anesthesia with I-653, halothane, isoflurane, and sevoflurane: A test of the effect of anesthetic concentration and duration in rats. Anesth Analg 66:977–982, 1987
4. Eger EI II: Stability of I-653 in soda lime. Anesth Analg 66:983–985, 1987
5. Koblin D, Eger EI II, Johnson B, Konopka K, Waskell L: I653 resists degradation in rats. Anesth Analg 67:534–538, 1988
6. Eger EI II, Johnson BH, Strum DP, Ferrell LD: Studies of the toxicity of I-653, halothane, and isoflurane in enzyme-induced, hypoxic rats. Anesth Analg 66:1227–1229, 1987
7. Panepinto LM, Phillips RW, Norden S, Pryor PC, Cox R: A comfortable, minimum stress method of restraint for Yucatan miniature swine. Lab Anim Sci 33:95–97, 1983
8. Drewes PA: Carbohydrates derivatives and metabolites, Clinical Chemistry: Principles and Techniques, 2nd edition. Edited by Henry RJ, Cannon DC, Winkelman JW. New York, Harper and Row, 1974, pp 1327–1334
9. Severinghaus JW: Blood gas calculator. J Appl Physiol 21:1108–1116, 1966
10. Willford DC, Hill EP: Modest effect of temperature on the porcine oxygen dissociation curve. Respir Physiol 64:113–123, 1986
11. Eger EI II, Johnson B, Weiskopf RB, Holmes MA, Yasuda N, Targ A, Rampil I: MAC of I653 and isoflurane: Definition of a supramaximal stimulus. Anesth Analg, in press
12. Lundeen G, Manohar M, Parks C: Systemic distribution of blood flow in swine while awake and during 1.0 and 1.5 MAC isoflurane anesthesia with or without 50% nitrous oxide. Anesth Analg 62:499–512, 1983
13. Eisele PH, Talken L, Eisele JH Jr: Potency of isoflurane and nitrous oxide in conventional swine. Lab Anim Sci 35:76–78, 1985
14. Weiskopf RB, Townsley MI, Riordan KK, Harris D, Chadwick K: Acid-base nomogram for swine blood. J Appl Physiol 54:978–983, 1983
15. Zar JH: Biostatistical Analysis. Englewood Cliffs, Prentice-Hall, 1974, pp 150–161
16. Weiskopf RB, Bogetz MS: Haemorrhage decreases the anaesthetic requirement for ketamine and thiopentone in the pig. Br J Anaesth 57:1022–1025, 1985
17. Weiskopf RB, Bogetz MS: Minimum alveolar concentrations (MAC) of halothane and nitrous oxide in swine. Anesth Analg 63:529–532, 1984
18. 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
19. Buffington CW, Romson JL, Levine A, Duttlinger NC, Huang AH: Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. ANESTHESIOLOGY 66:280–292, 1987
20. Priebe H-J, Foex P: Isoflurane induces regional myocardial dysfunction in dogs with critical coronary artery stenosis. ANESTHESIOLOGY 66:293–300, 1987