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Individual Organ Contributions to the Decrease in Whole-body $\dot{V}_{O_2}$ with Isoflurane

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The present study was designed to determine whether there were differences between the effects of isoflurane and halothane on canine whole-body and individual organ oxygen uptake ($\dot{V}_O$). Whole-body $\dot{V}_{O_2}$ and myocardial, splanchnic, renal, and skeletal muscle $\dot{V}_{O_2}$'s were determined at isoflurane concentrations equivalent to those used in a previous study with halothane. With increases in isoflurane, whole-body $\dot{V}_{O_2}$ decreased progressively. As with halothane, the major component of the decrease was a reduction in myocardial $\dot{V}_{O_2}$ that was related to a reduction in cardiac output and arterial blood pressure; contributions from other organs were minor. No significant difference between the effects of isoflurane and halothane on whole-body or individual organ $\dot{V}_{O_2}$'s was found. These findings support the view that anesthetic agents are not general metabolic depressants and that observed changes in whole-body $\dot{V}_{O_2}$ reflect the summated changes in individual organ $\dot{V}_{O_2}$'s occasioned by an anesthetic-induced change in organ function and metabolic requirements. (Key words: Anesthetics, volatile: isoflurane; Oxygen: consumption; Heart: oxygen consumption; Kidney: oxygen consumption; Muscle, skeletal: oxygen consumption.)

WE HAVE ESTABLISHED that the major portion of the decrease in whole-body oxygen uptake ($\dot{V}_{O_2}$) during halothane anesthesia is due to the decrease in myocardial $\dot{V}_{O_2}$ that results from the large reduction in cardiac output and arterial blood pressure with halothane.[1] Because isoflurane (Forane‡) anesthesia in man is reportedly associated with only minor, insignificant reductions in cardiac output,[2] it was of interest to determine whether the pattern of whole-body and organ $\dot{V}_{O_2}$ changes with isoflurane differs from that with halothane. We accordingly determined canine whole-body, myocardial, splanchnic, renal, and skeletal muscle $\dot{V}_{O_2}$'s at equivalent levels of isoflurane anesthesia. The decreases in whole-body and individual organ $\dot{V}_{O_2}$'s with isoflurane were similar to those seen with halothane, the decrease in myocardial $\dot{V}_{O_2}$ providing the major contribution; other organ systems made only minor contributions.

Materials and Methods

In all studies, unpremedicated dogs were anesthetized with isoflurane in O_2 and N_2 and the tracheas intubated with the aid of succinylcholine (20 mg), which was continued thereafter at 150 mg/h. Ventilation was provided by a Harvard pump and nonrebreathing system; appropriate adjustments of $F_{I_{O_2}}$ and ventilatory volume maintained $P_{a_{O_2}}$'s and $P_{a_{CO_2}}$'s at 150 ± 5 and 40 ± 2 mm Hg, respectively (means ± SE). The concentration of isoflurane (end-expired) was determined by infrared analysis. Body and organ temperatures were maintained at 37.0 ± 0.2 C by external measures. Pressures were transduced by strain gauge. Blood-gas values were measured by electrodes at 37.0 C. The blood O_2 content was calculated from the P_{O_2} and the oxyhemoglobin concentration (IL CO-Oximeter). Whole-body and regional and organ $\dot{V}_{O_2}$'s were calculated by means of the Fick equation; appropriate values were used for blood flow rates ($\dot{Q}$) and the arteriovenous oxygen-content differences [$(A\text{-}V)_{O_2}$] and

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TABLE 1. Metabolic and Hemodynamic Responses to Isoflurane (Ten Dogs, 37 C)

	Isoflurane, End-expired (Per Cent)							
	0.4		1.4		1.9		2.6	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
$\dot{V}_{O_2}$, whole-body (ml/min/kg)	6.34	0.28	5.70*	0.19	5.39*	0.22	4.93*	0.26
$\dot{V}_{O_2}$, myocardial (ml/min/kg)	1.37	0.12	0.98*	0.08	0.83*	0.06	0.68*	0.04
$\frac{\dot{V}_{O_2} \text{ myocardial}}{\dot{V}_{O_2} \text{ whole-body}}$	0.21	0.02	0.17*	0.01	0.15*	0.01	0.14*	0.01
$\dot{Q}$ (ml/min/kg)	221	26	168*	18	148*	14	128*	14
Pressures (mean, mm Hg)								
Systemic (arterial)	115	4	95*	3	85*	4	70*	2
Pulmonary (arterial)	18	2	15*	1	14*	1	13*	1
Right atrial	2	0	2	0	2	0	2	0
External work (kg-m/min)								
Left ventricle	5.87	0.72	3.75*	0.47	2.97*	0.41	2.11*	0.27
Right ventricle	0.98	0.21	0.60*	0.10	0.48*	0.07	0.39*	0.05
Heart rate (beats/min)	119	6	120	9	123	5	122	4

* Significantly different ($P < 0.05$) from 0.4 per cent value by t test for paired data.

were expressed relative to whole-body weight as determined prior to induction of anesthesia. Sequential determinations of $\dot{V}_{O_2}$ did not differ by more than 10 per cent, and the overall, average difference was 4 per cent. Left and right ventricular external work were calculated from total $\dot{Q}$ and mean systemic and pulmonary arterial pressures, respectively, and a constant, as previously described.[3] At autopsy, catheter positions were confirmed and organ weights were determined. MAC values for halothane and isoflurane in dogs of 0.87 and 1.48 per cent, respectively, were the reference points for establishing equivalent anesthetic concentrations[4] over the range of concentrations used.

The effects of isoflurane on whole-body metabolism and hemodynamics were determined in ten dogs (weights: whole-body, 16 ± 1 kg; heart, 110 ± 10 g). Catheters were placed in the carotid and pulmonary arteries, right atrium, and outflow tract of the right ventricle for measurement of pressures, determination of $\dot{Q}$ (indocyanine green dye dilution technique), and sampling of arterial and mixed venous blood. Observations were made in triplicate at isoflurane concentrations of 0.4, 1.4, 1.9, and 2.6 ± 0.1 per cent (mean ± SE) in this sequence and, in alternative dogs, in the reverse sequence. (For convenience, results are presented only in terms of increasing concentration.) At each isoflurane concentration 1 hour was allowed to elapse, the first 30 minutes being for stabilization and the second 30 minutes for observations. Myocardial $\dot{V}_{O_2}$'s during these studies were calculated from the observed values for external work in this study and from the relationship between myocardial external work and $\dot{V}_{O_2}$ established in the following study.

The relationship between myocardial external work and $\dot{V}_{O_2}$ during isoflurane anesthesia was determined in eight additional dogs (weights: whole-body, 20 ± 3 kg; heart, 143 ± 30 g). Right-heart bypass was established after ligation of the azygos vein, appropriate cannulations of the right atrium, superior vena cava (SVC), inferior vena cava (IVC), and pulmonary trunk, and arrangements with an extracorporeal apparatus that included a reservoir, pump, and heat exchanger. In this technique, SVC, IVC, and myocardial drainages are isolated, which permits determinations of $\dot{Q}$, $(A\text{-}V)_{O_2}$, and $\dot{V}_{O_2}$ for each.[3] $\dot{Q}$ was measured directly by timed collection in a graduated cylinder. Observa-

tions were made in triplicate at isoflurane concentrations of <0.3, 1.4, and 2.6 per cent. At each concentration, left ventricular work was arranged to approximate that observed in the preceding study by appropriate modifications of blood volume and flow rates for the right-heart bypass pump.

Splanchnic and renal $\dot{V}_{O_2}$'s (six dogs) and gastrocnemius–plantaris muscle $\dot{V}_{O_2}$'s (bilateral, six dogs) were determined at isoflurane concentrations of 0.4 and 2.6 per cent by surgical methods that provide for separation, direct collection, quantitation, and return of the venous blood flow from these organs.[5–7]

Results

The whole-body metabolic and hemodynamic responses to increases in the isoflurane concentration are summarized in table 1. In this and in subsequent presentations, organ $\dot{V}_{O_2}$ values are expressed relative to whole-body weight for convenience of developing the whole-body profile in compatible units. There was no significant differences between values at 0.4 per cent isoflurane and those observed previously at 0.2 per cent halothane.[1] With increased isoflurane concentrations, whole-body and myocardial $\dot{V}_{O_2}$'s, $\dot{Q}$, arterial pressures, and myocardial external work decreased progressively in a manner similar to that observed with halothane (table 2). Although isoflurane tended to produce smaller decreases in whole-body and myocardial $\dot{V}_{O_2}$'s, $\dot{Q}$, and myocardial external work, no statistically significant difference was established. However, when the results of this and other studies[1,8] were pooled, $\dot{Q}$ was significantly greater ($P < 0.02$) at equivalent concentrations of isoflurane than with halothane ($\dot{Q}$,

TABLE 2. Relative Changes (Percentage of Control) in Canine Metabolism and Hemodynamics with Increases to Equivalent Concentrations of Isoflurane (2.6 Per Cent) and Halothane (1.5 Per Cent)

	Isoflurane*	Halothane†
$\dot{V}_{O_2}$, whole-body	78	73
$\dot{V}_{O_2}$, myocardial	50	41
$\dot{Q}$	58	51
Arterial pressure	61	57
External work, total	36	30
Heart rate	103	105

* Data from present study.
† Adapted from Theye.[1]

TABLE 3. Myocardial and Regional Metabolic and Hemodynamic Responses to Insoflurane (Eight Dogs, 37 C)

	Isoflurane, End-expired (Per Cent)					
	<0.3		1.4		2.6	
	Mean	SE	Mean	SE	Mean	SE
$\dot{V}_{O_2}$ (ml/min/kg)						
Whole-body	6.63	0.17	5.80*	0.23	5.15*	0.15
SVC drainage	1.61	0.07	1.45	0.08	1.37*	0.07
IVC drainage	3.95	0.15	3.64	0.16	3.29*	0.10
Myocardial	1.07	0.06	0.71*	0.04	0.49*	0.02
$\dot{Q}$ (ml/min/kg)						
Whole-body	154	4	128*	3	108*	3
SVC drainage	47	3	41	2	33*	2
IVC drainage	98	3	79*	2	70*	2
Myocardial	9	2	8	1	5*	1
Arterial pressure (mean, mm Hg)	151	5	99*	6	69*	4
External work, LV (kg-m/min)	6.68	0.26	3.63*	0.23	2.15*	0.10

* Significantly different ($P < 0.05$) from <0.3 per cent value by t test for paired data.

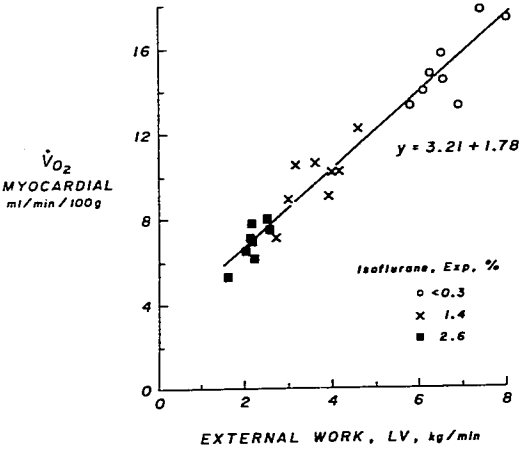

FIG. 1. Relationship between left ventricular external work and myocardial $\dot{V}_{O_2}$ at three different isoflurane concentrations. Note the direct relationship and lack of effect of isoflurane concentration on the relationship.

ml/min/kg at MAC [mean ± SE]: isoflurane, 176 ± 13; halothane, 132 ± 11).

The myocardial and other regional metabolic and hemodynamic responses to isoflurane are summarized in table 3. Overall, the decreases in $\dot{V}_{O_2}$ were similar to those of the whole-body studies and the decreases in the regional drainages were similar to those observed with halothane.[3] The mean arterial pressure at the lowest isoflurane concentration was greater in this study (151 mm Hg) than in the whole-body study (115 mm Hg), presumably because of a lower concentration of isoflurane (<0.3 and 0.4 per cent, respectively). The values for left ventricular work in this study spanned the range of those observed in the whole-body study (fig. 1). There was a direct relationship between left ventricular external work (x) and myocardial $\dot{V}_{O_2}$ (y) during isoflurane anesthesia [y = 3.21 + (1.78 × ± 0.09)], which was not significantly different from that previously observed with halothane [y = 1.44 + (2.13 × ± 0.29)].[3] The relationship between external work and $\dot{V}_{O_2}$ was not modified by the concentration of isoflurane, except, of course, as the latter altered external work (fig. 1).

The effects of isoflurane on splanchnic, renal, and skeletal muscle $\dot{V}_{O_2}$'s and on hemodynamics are summarized in table 4. For convenience of this presentation, the findings in the gastrocnemius–plantaris muscle group (weight, 38 ± 13 g) have been extrapolated to whole-body skeletal muscle $\dot{V}_{O_2}$; for this, we used the same assumptions applied previously with halothane (0.4 per cent value, 35 per cent of whole-body $\dot{V}_{O_2}$; 2.6 per cent value, based on the 16 per cent decrease in $\dot{V}_{O_2}$ observed in the muscle studied).[1] Splanchnic, renal, and skeletal muscle $\dot{V}_{O_2}$'s decreased by 7, 27, and 16 per cent, respectively. Blood flow was maintained well in these regions, and the decreases in $\dot{V}_{O_2}$ could not be related to deficiencies in O_2 transport.

The effects of isoflurane and halothane on whole-body and regional $\dot{V}_{O_2}$ at equivalent conditions are summarized in table 5. The isoflurane projections are based on data of the present study and an additional study of the effects of isoflurane on canine cerebral metabolism, in which a 30 per cent decrease in cerebral metabolic rate occurred with 2.4 per cent isoflurane.[9] These findings were extrapolated to the whole brain by means of the same assumptions applied previously

TABLE 4. Effects of Isoflurane on Splanchnic, Renal, and Skeletal Muscle $\dot{V}_{O_2}$'s and on Hemodynamics

	Isoflurane, End-expired (Per Cent)			
	0.4		2.6	
	Mean	SE	Mean	SE
$\dot{V}_{O_2}$ (ml/min/kg)				
Splanchnic	2.06	0.08	1.91*	0.13
Renal	0.41	0.02	0.30*	0.04
Skeletal muscle	2.22	0.14	1.86*	0.15
Blood flow (ml/min)†				
Splanchnic	487	67	466	62
Renal	349	46	293	42
Skeletal muscle	6.7	0.9	8.1	0.9
Arterial blood pressure (mean, mm Hg)	117	4	71*	2

* Significantly different ($P < 0.05$), t test for paired data.
† Actual flows of organs being studied.

with halothane.[1] Overall, there was a remarkable similarity in the changes of whole-body and regional $\dot{V}_{O_2}$'s with isoflurane and halothane. With each, the myocardial component was the major contributor to the whole-body decrease, with lesser contributions from the other organs.

Discussion

These findings are in substantial agreement with those of a previous study.[8] They collectively suggest that isoflurane, compared with halothane, produces a smaller decrease in cardiac output and similar decreases in arterial blood pressure and $\dot{V}_{O_2}$ in dogs at equivalent anesthetic concentrations. We have not observed in either study an increase in heart rate that was sufficient to prevent a decrease in cardiac output with isoflurane, as observed in man by Stevens and associates.[2] However, we would agree with these investigators that whole-body and regional blood flows are qualitatively better maintained with isoflurane than with halothane at equivalent levels of anesthesia.

The changes in regional and whole-body $\dot{V}_{O_2}$'s with isoflurane are not significantly different from those with halothane.[1] These findings confirm for isoflurane those previously established for halothane—that anesthetics are not universal metabolic depressants—and support our contention that anesthetic-induced changes in $\dot{V}_{O_2}$ should be viewed as reflections of altered metabolic requirements resulting from anesthetic-induced changes in organ function.

Cohen[10] has asked whether alterations in myocardial external work and $\dot{V}_{O_2}$ associated with anesthetic agents represent altered myocardial efficiency. This question cannot

TABLE 5. Effects of Isoflurane and Halothane on Canine Whole-body and Regional $\dot{V}_{O_2}$

	$\dot{V}_{O_2}$ (ml/min/kg*)			
	Isoflurane (Per Cent)†		Halothane (Per Cent)‡	
	0.4	2.6	0.2	1.5
Whole-body	6.34	4.93	6.46	4.71
Myocardial	1.37	0.68	1.40	0.57
Splanchnic	2.06	1.91	1.78	1.62
Renal	0.41	0.30	0.42	0.33
Cerebral	0.20	0.14	0.22	0.18
Skeletal muscle	2.22	1.86	2.26	1.85
Other tissues (difference)	0.08	0.04	0.38	0.16

* Whole-body weight.
† Data from present study
‡ Adapted from Theye.[1]

yet be answered definitively; it may be a meaningless question. For example, if myocardial efficiency is defined simply as the ratio of myocardial external work and $\dot{V}_{O_2}$, and if anesthetics generally lessen myocardial work and $\dot{V}_{O_2}$ in the manner established for halothane and isoflurane, then the ratio will become smaller as work is decreased with anesthesia; thus, anesthetics could be said to reduce myocardial efficiency. This diminution in the ratio with a decrease in work, however, merely reflects the fact that extrapolation of the regression line relating work and $\dot{V}_{O_2}$ does not go through the point of zero work and zero $\dot{V}_{O_2}$ but, rather, touches zero work at a $\dot{V}_{O_2}$ of approximately 2 ml/min/100 g. This extrapolation is compatible with the knowledge that the living heart doing no measurable external work (*e.g.*, ventricular fibrillation and cardiac asystole) continues to expend energy and consume O_2,[11] but it does limit the interpretation of simply a change in the ratio of work to $\dot{V}_{O_2}$. Moreover, as Burton[12] has pointed out, this simplistic analysis is rather meaningless because the external work is a trivial item in the total energy exchange of the heart and actual efficiency values are small (as low as 3 per cent) and never more than 10 to 15 per cent. It is accordingly of greater significance to note that the relationships between myocardial external work and $\dot{V}_{O_2}$ were not significantly different for halothane and isoflurane and that there was no indication that isoflurane concentration by itself influences this relationship.

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