The Contributions of Individual Organ Systems to the Decrease in Whole-body $\dot{V}_O_2$ with Halothane

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Whole-body and myocardial $\dot{V}_O_2$ were estimated in dogs during anesthesia with halothane at <0.2, 0.8, 1.1, and 1.5 per cent end-expired halothane. These observations were used with earlier estimates of the effects of halothane on skeletal muscle, splanchnic, renal, and cerebral $\dot{V}_O_2$ to define the relative contributions of individual organs to the overall decrease in whole-body $\dot{V}_O_2$. Whole-body $\dot{V}_O_2$ decreased 27 per cent as halothane was increased from <0.2 to 1.5 per cent end-expired. This was due primarily to a decrease in myocardial $\dot{V}_O_2$ resulting from decreased cardiac output and arterial pressure. Contributions of individual organs to the total decrease in whole-body $\dot{V}_O_2$ expressed as percentages, were: myocardial, 47; skeletal muscle, 23; splanchnic, 9; renal, 5; cerebral, 2. Thus, 86 per cent of the total decrease in whole-body $\dot{V}_O_2$ was accounted for, the remainder presumably occurring in tissues not studied (skin, bone, salivary glands, spinal cord, lung, and others). (Key words: Halothane; Oxygen consumption.)

A major goal of this laboratory has been to define the contribution of each organ to the total decrease in whole-body oxygen consumption rate ($\dot{V}_O_2$) which occurs with halothane. The dog has been used for these studies because of ready availability, acceptability of the necessary invasive techniques, and established methods of study of individual organs. We previously quantitated the changes in whole-body, cerebral, renal, skeletal muscle, and splanchnic $\dot{V}_O_2$ with halothane, and we also established a direct relationship between myocardial external work and myocardial $\dot{V}_O_2$, during anesthesia with halothane. The present study provides estimates of total myocardial external work and $\dot{V}_O_2$ during halothane anesthesia and, thereby, completes the information necessary to project (by organ) the individual components of the decrease in whole-body $\dot{V}_O_2$ with halothane.

Material and Methods

Unpremedicated fasting dogs (weights 20 ± 2 kg) were anesthetized with halothane. The tracheas were intubated with the aid of succinylcholine (20 mg), which was continued thereafter at 150 mg/hr. Ventilation with oxygen and halothane (1.5 per cent end-expired, infrared analyzer) was maintained by a Harvard pump, adjusted to result in a $P_{O_2}$ of 40 ± 2 mm Hg (electrodes, 37 C). Body temperature (esophageal thermistor) was maintained at 37.0 ± 0.2 by external means. These conditions, including succinylcholine dosage, were the same as those in previous studies of the other organ systems. Arrangements were provided for measurement of whole-body $\dot{V}_O_2$ in the presence of halothane in $O_2$ by closed-circuit spirometry. Catheters were placed in the femoral artery, pulmonary artery, and right atrium for measurement of pressures (strain gauge) and withdrawal of arterial and mixed venous blood samples for determination of blood $O_2$ content and buffer base.

After these preparations, sequential observations were made under the following conditions: Equilibration was achieved with <0.2, 0.8, 1.1, and 1.5 per cent halothane or, in alternate dogs, 1.5, 1.1, 0.8, and <0.2 per cent halothane, 30 minutes elapsing at each new concentration prior to the observations, which occupied a further 30 minutes. At each con-
centration, whole-body $\dot{V}O_2$ was measured over two 10-minute intervals. Before and after each determination, the arterial–mixed venous $O_2$ content difference $\dot{(A-V)}O_2$ was determined in triplicate; pressures, heart rate, and blood gases were determined in duplicate. From these, cardiac output was calculated from $\dot{V}O_2$ and $\dot{(A-V)}O_2$ by the Fick formula. External work was calculated for the left ventricle and for the right ventricle by substitution of mean pulmonary for mean systemic arterial pressure, as previously described. $\dot{V}O_2$'s (ml/min) for the left and right myocardium were estimated from these values for external work, using the relationships previously observed during halothane anesthesia and similar experimental conditions, suitably corrected to reflect the average heart weight of 146 g in the previous study. $\dot{V}O_2$'s for both the whole body and the total myocardium were expressed relative to whole-body weight (kg), as determined in the immediate preanesthetic period.

For convenience, all results at each concentration have been pooled and are presented in order of increasing concentrations rather than the actual order of the individual experiments.

### Results

**Myocardial $\dot{V}O_2$**

Whole-body and myocardial $\dot{V}O_2$ decreased progressively as the halothane concentration in each dog was increased from 0.2 to 1.5 per cent. These changes were reversed in the progression from 1.5 to 0.2 per cent. Pooled observations at each concentration are presented in table 1, without regard to the initial and final halothane concentrations. Overall, the decreases occurring in whole-body and myocardial $\dot{V}O_2$'s with an increase in halothane from 0.2 to 1.5 per cent were approximately 27 and 59 per cent, respectively. Over this range, the decrease in $\dot{V}O_2$ was greater for the myocardium than for the whole body, and the relative contribution of myocardial to whole-body $\dot{V}O_2$ decreased from 22 to 12 per cent. The decrease in myocardial $\dot{V}O_2$ reflected a reduction in the external work of both right and left ventricles, resulting from progressive reductions in cardiac output, systemic arterial pressure, and pulmonary arterial pressure, as the halothane concentration increased. The reduction in cardiac output was accompanied by a modest increase in

### Table 1. Effects of Halothane on Canine Metabolism and Circulation (Eight Dogs, 37 C)

<table>
<thead>
<tr>
<th></th>
<th>Halothane, End-expired (Per Cent)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>$\dot{V}O_2$, whole-body (ml/min/kg)</td>
<td>6.46</td>
</tr>
<tr>
<td>$\dot{V}O_2$, myocardial (ml/min/kg)</td>
<td>1.40</td>
</tr>
<tr>
<td>$\dot{V}O_2$ total</td>
<td>0.22</td>
</tr>
<tr>
<td>$\dot{Q}$ (l/min)</td>
<td>3.43</td>
</tr>
</tbody>
</table>

**Pressures (mean, mm Hg)**

|                          | 134      | 111*     | 96*      | 75*      | 5*       |
| Systemic (arterial)      | 10       | 12*      | 11*      | 12*      |
| Pulmonary artery         | 3        | 3        | 4*       | 5*       |
| Right atrium             |          |          |          |          |

**External work (kg-m/min)**

|                          | 0.72     | 3.85*    | 3.58     | 3.12     | 1.97*    | 0.29     |
| Left ventricle           | 0.81     | 0.45*    | 0.36*    | 0.36*    | 0.30*    | 0.04     |
| Right ventricle          |          |          |          |          |

**Heart rate (beats/min)**

|                          | 111      | 121      | 121      | 121      | 117      | 4        |

*Significantly different ($P < 0.05$) from <0.2 per cent value by t test for paired data.
right atrial pressure and was, therefore, apparently based upon lessened contractility rather than diminished filling pressure. Heart rates were similar at all concentrations, which suggests that experimental conditions at <0.2 per cent halothane did not provoke unusual degrees of excitement and distress. Arterial blood PO₂ and buffer base did not change significantly with increase in halothane and, overall, were 490 ± 10 mm Hg and 48 ± 1 mEq/l, respectively (mean ±SD).

**OTHER ORGANS AND DECREASE IN WHOLE-BODY V̇O₂**

These findings were combined with observations from previous studies in the preparation of table 2, which provides an estimate of the relative contributions of the major organ systems to the total decrease in whole-body V̇O₂. In this projection, splanchnic V̇O₂ values are as originally presented. Changes in renal V̇O₂ are as originally described, the units being appropriately rearranged to reflect an average total renal weight of 90 g in a dog weighing 20 kg. Changes in cerebral V̇O₂ are presented to represent a 17 per cent reduction in cerebral V̇O₂ at 0.8 per cent halothane, without further reductions at greater concentrations, the units being rearranged by assuming an average total brain weight of 80 g in a dog weighing 20 kg. For skeletal muscle, the <0.2 per cent value was arbitrarily assigned to be 35 per cent of whole-body V̇O₂, since this is the approximate average of various indirect estimates for man and the ratios of skeletal-muscle mass to whole-body mass for dog and man are approximately the same (40 per cent). Subsequent reductions in skeletal muscle V̇O₂ were extrapolations of actual percentage reductions observed in canine gastrocnemius muscle during similar experimental conditions. Finally, V̇O₂ in other tissues was obtained by difference and is, thereby, a composite both of events in such unstudied individual tissues as skin, bone, salivary glands, spinal cord, and lung and of the errors of experiment and projection involved in obtaining the other projected values.

The changes in whole-body and regional V̇O₂ with halothane evident in table 2 were used in the preparation of figure 1 and table 3. At 1.5 per cent end-expired halothane, nearly 90 per cent of the total reduction in whole-body V̇O₂ resulted from decreases in V̇O₂ of specific organs; also, the decrease in myocardial V̇O₂ accounted for nearly 50 per cent of the total decrease in whole-body V̇O₂.

**Discussion**

During the first half of this century, there was much interest in the effects of anesthetics on metabolism and whole-body V̇O₂. Anesthesia was then considered to be a sequel of a generalized reduction in cerebral metabolic activity, and it was expected that all anesthetics would decrease tissue V̇O₂ both in vivo and in vitro. The clinical implications of this were pursued by Guebel, who believed that the anesthetic state could be equated with a certain level of metabolic activity. He concluded that factors which influenced the
concentration of anesthetic necessary for a
given anesthetic state, such as premedication
and age, did so because of their individual
effects on metabolic activity, which were then
summatied with those of the anesthetic. De-
spite vigorous efforts by various investigators
during this period, no evidence was obtained
to support a unified concept of the relation-
ship between the state of anesthesia and meta-
abolic rate.11

This earlier view has now largely been dis-
carded; it has been replaced by the concept
that the anesthetic state reflects altered cee-
bral function, which may or may not result in
altered whole-body or cerebral $V_\text{O}_2$. Major
credit for this must be given to Ketey and
Schmidt.12 They developed and validated the
nitrous oxide technique for measuring cere-ral blood flow which, when combined with
cerebral $(A-V)_{O_2}$, provided reliable estimates
of cerebral $V_\text{O}_2$ for the first time. Studies by
these pioneers, their associates, and others
indicated that altered cerebral states such as
sleep and schizophrenia were not associated
with change in cerebral $V_\text{O}_2$. Furthermore,
while certain anesthetics, notably thiopental,
were capable of inducing dose-related reduc-
tions in cerebral $V_\text{O}_2$, others, particularly
ether and cyclopropane, had an effect which
on occasion was biphase, with an apparent
increase in cerebral $V_\text{O}_2$ at higher concen-
trations.13 Meanwhile, the parallel investiga-
tion of the effects of anesthetics in whole-body $V_\text{O}_2$
was aided by the availability of new tech-
niques for the determination of gas and blood
$O_2$ content in the presence of volatile anes-
thetic agents. These studies established that
the anesthetic state in man is not necessarily
associated with a reduction in whole-body
$V_\text{O}_2$; that whereas thiopental alone results in
a decrease in $V_\text{O}_2$, ethyl ether alone leads to
an increase in $V_\text{O}_2$, and, finally, that in pre-
dicting $V_\text{O}_2$, many factors must be considered
in addition to the actual anesthetic agent being
used, including premedication, relaxants, body
temperature, and degree of skeletal muscle
activity.14,15

Our findings add another dimension by pro-
viding an analysis, by individual organs, of
the summated contributions to the whole-body
decreases in $V_\text{O}_2$ which occur with increasing
concentration of halothane. Immediately evi-
dent is the demonstration that not all tissues
contribute to the overall reduction in $V_\text{O}_2$ to
the same extent. Furthermore, neither relative
mass nor relative resting $V_\text{O}_2$, alone or in com-

In preparing the estimates of total myo-
cardial $V_\text{O}_2$, during the present study, it is recog-
nized that myocardial $V_\text{O}_2$ cannot be accu-
 rately predicted for all circumstances from
 any single manifestation of cardiac activity.
There are proponents of a variety of indices,
including myocardial external work, the pro-
 duct of heart rate and arterial blood pressure,
the area under the ventricular systolic pres-
 sure curve (tension-time index), and the
maximal velocity of myocardial isotonic short-
ening.17-19 Confidence in the use of external
work as the best available estimate of $V_\text{O}_2$
for the present study arises from several con-
 siderations. In previous studies4 providing
direct measurements of total coronary blood
flow and coronary $(A-V)_{O_2}$, our laboratory
established that during halothane anesthesia
canine left ventricular $V_\text{O}_2$ (ml/min/100 g)
and left ventricular external work (kg-m/min)
are directly related, as expressed by the equa-
tion:

$$V_{\text{O}_2} = \text{work} \times 2.1 + 1.4.$$  

More than 80 per cent of the external work
values of the present study were within the
range of those in this previous study. The
general validity of this relationship for the
dog is supported by the similarity of $V_{\text{O}_2}$
values derived either by substituting the mean
value for canine basal left ventricular external
work (3.8 kg-m/min) in this expression,
yielding 9.4 ml/min/100 g, or by calculating
canine basal left ventricular $V_{\text{O}_2}$ using mean
values for left coronary blood flow (79 ml/min/100 g) and the coronary (A-V)O_2 (12.5 ml/min/100 ml), yielding 9.9 ml/min/100 g. Furthermore, the values for total myocardial O_2 in the present study are reasonable when compared with those obtained by others in dogs using different experimental approaches. For example, Harrison and associates, studying dogs similar in body weight and total O_2 to those of the present study but sedated with large doses of morphine, found these mean values for 23 experiments with the chest closed*: cardiac output, 1.7 l/min; mean arterial pressure, 118 mm Hg; total myocardial external work, 3.78 kg-m/min; total myocardial O_2, 0.73 ml/kg. Comparable values for the control period from the present study are 3.4 l/min, 134 mm Hg, 7.53 kg-m/min, and 1.40 ml/min/kg, respectively; the initial myocardial O_2, which was approximately twice as great, was matched with a twice greater initial external work and cardiac output. Furthermore, with an increase in halothane to 1.1 per cent and a consequent reduction in total external work to 3.48 kg-m/min, the estimated value for total myocardial O_2 was 0.77 ml/min/kg in our study, and both of these values are acceptably close to the control values of Harrison and associates.

The basic premise of the present study—that, in the dog anesthetized with halothane, reduction in myocardial O_2 is the major component in the decrease in whole-body O_2—is supported not only by the projected values of the present study but also by the findings of our early exploratory studies in dogs. In the latter, the decreases in whole-body O_2 with increasing concentrations of halothane could be approximately duplicated without change in halothane concentration by measures that reduced arterial pressure and cardiac output (vagal stimulation, paired pulse stimulation).

*In this reference, the heading in table 3 regarding chest "open" or "closed" has been accidentally and incorrectly switched.

**TABLE 3. Percentage Contributions of Organs to the Total Decrease in Whole-body O_2 during an Increase in from <0.2 to 1.5 Per cent End-expired Halothane**

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Decrease (Per Cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial</td>
<td>47</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>23</td>
</tr>
<tr>
<td>Splanchnic</td>
<td>0</td>
</tr>
<tr>
<td>Renal</td>
<td>5</td>
</tr>
<tr>
<td>Cerebral</td>
<td>2</td>
</tr>
<tr>
<td>Other tissues</td>
<td>14</td>
</tr>
</tbody>
</table>
and could be reversed at the greater halothane concentrations by measures which increased arterial pressure and cardiac output (digitalis and increased blood volume). Although changes in renal and splanchnic $V_{O_2}$ may also have contributed to the overall changes observed with these maneuvers, the change in myocardial external work and $V_{O_2}$ would now seem to have been the major contribution. The basic premise is supported also by our failure to account in any other way for the total change in whole-body $V_{O_2}$ which occurs with halothane. The effects of halothane on $V_{O_2}$'s of all of the other major organs have been studied; the total, cumulative effect on all of these (splanchnic, renal, cerebral, and skeletal muscle) is only approximately 39 per cent of the total change in whole-body $V_{O_2}$.

In each study directed toward a single organ, experimental conditions and measurement techniques were approximately similar to those used in all of the other studies. Control and experimental values for each organ were approximately the same as those observed by others using the same or different techniques for studying the organ. The proportion of total whole-body $V_{O_2}$ unaccounted for in the summed projections of individual organs is small and is insufficient in itself to suggest a major contribution which has been overlooked.

It now seems clear that the older idea that all anesthetics are general metabolic depressants should be replaced by the view that no particular relationship between the anesthetic state and total or cerebral metabolic activity exists, and that generalizations are inappropriate. Furthermore, for anesthesia associated with a decrease in whole-body $V_{O_2}$, it is unwise to presume that all organs contribute to the total change in any prorated manner other than in the circumstance of general hypothermia without shivering.

References

4. Theye RA: Effect of halothane on canine gas-
12. Cuedel AE: Metabolism and reflex irritability in anesthesia. JAMA 83:1730-1738, 1924