The Effects of Halothane on Canine Renal Function and Oxygen Consumption

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The effects of halothane on renal function and consumption of oxygen ($\dot{V}_{O_2}$) have been studied in dogs, with and without diuresis. With diuresis induced by a variety of intravenous solutions and infusion rates, urinary flow rates during halothane anesthesia were relatively low and urine had an osmolality approximately twice that of plasma. Increasing halothane had little effect on this or other aspects of renal function, including glomerular filtration rate, renal blood flow, and the relation between tubular reabsorption of sodium and nonbasal renal $\dot{V}_{O_2}$. Approximately 28 equivalents of sodium were reabsorbed per mole of nonbasal oxygen consumed, which is the value observed by others in a variety of other situations. Conditions of the nondiuresis situation were similar to those under which whole-body, myocardial, cerebral, and skeletal muscle $\dot{V}_{O_2}$ previously were demonstrated to be decreased with increased halothane. Renal $\dot{V}_{O_2}$ in this situation was 7 to 8 per cent of whole-body $\dot{V}_{O_2}$ and was little changed by increasing halothane from 0.1 to 1.5 per cent. (Key words: Halothane; Renal function; Renal $\dot{V}_{O_2}$; Antidiuresis.)

ONE OF THE GOALS of this laboratory has been to establish the effects of halothane on $\dot{V}_{O_2}$ of each organ of the body and thus, ultimately, to account for the total decrease in whole-body $\dot{V}_{O_2}$ observed with halothane.[1] Heart, brain, and skeletal muscle have been studied, and of the major organs only the kidney and liver remain to be examined. The present study is concerned with the kidney, which consumes approximately 8 per cent of the total $\dot{V}_{O_2}$ of man at rest.[2] Recent studies in other animals have established that total renal $\dot{V}_{O_2}$ consists of a basal $\dot{V}_{O_2}$, occurring during anuria in the absence of glomerular filtration and tubular reabsorption, and an additional component, termed "nonbasal renal $\dot{V}_{O_2}$," which is related directly to the amount of sodium reabsorbed by renal tubules. This has been established to be a quantitative relationship and, in varous circumstances, approximately 28 equivalents of sodium are reabsorbed for each mole of nonbasal O_2 consumed. Accordingly, the present studies were designed to determine the effect of halothane on total renal $\dot{V}_{O_2}$, the relation between sodium reabsorbed and nonbasal $\dot{V}_{O_2}$, and the effect of halothane concentration on this relationship.

Methods

Unpremedicated female dogs weighing 20 ± 3 kg were anesthetized with halothane and their tracheas were intubated with the aid of succinylcholine (20 mg). Administration of succinylcholine was continued at a rate of 150 mg/hr. Ventilation by Harvard pump with O_2 in N_2 and halothane as desired was adjusted to result in a Pa_{CO_2} of 40 ± 2 mm Hg with the relative concentration of O_2 adjusted to result in a Pa_{O_2} of 140 ± 10 mm Hg. Esophageal temperature was maintained at 37.0 ± 0.2 C by external means. The femoral artery was cannulated for sampling and measurement of blood pressure by strain gauge. The external jugular and other superficial veins were cannulated for intravenous administration of fluids, return of blood, and passage of catheters. In studies of the right kidney utilizing only clearance techniques, a catheter was placed in the right renal vein with fluoroscopic guidance and, after laparotomy, a catheter was fixed in the right ureter. In all other studies, both kidneys were studied collectively with urine drained by catheter from the bladder.

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TABLE 1. Effects of Halothane on Renal $\dot{V}_{O_2}$ and Hemodynamics (Nondiuresis, Five Dogs)

	Expired Halothane (Per Cent) (± 0.1)							
	0.1		0.8		1.1		1.5	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
$\dot{V}_{O_2}$ (mmole/min/100 g)	0.42	0.08	0.38	0.08	0.35	0.07	0.33	0.06
Renal blood flow (ml/min/100 g)	565	39	555	49	503	60	461	58
Arterial pressure, mean (mm Hg)	142	3	116*	7	107*	6	93*	5
Urinary flow (ml/min)	0.41	0.13	0.60	0.27	0.38	0.20	0.14*	0.08

* Significantly different ($P < 0.05$) from 0.1 per cent value by Student's t test for paired data.

For diuresis, dogs received one liter of either Ringer's solution or 5 per cent glucose in distilled water 6 to 18 hours prior to study and an additional liter of the same solution during the one to two hours of preparation. During the studies, fluids were given intravenously at steady rates that varied from 6 to 15 ml/min between dogs and consisted of either one of the aforementioned solutions or a mixture of ⅓ Ringer's solution in distilled water with 25 gm of glucose added per liter. While none of these approaches resulted in diuresis of the magnitude expected, urinary flow rates were at least 2 ml/min and were adequate for the use of conventional clearance techniques. In the nondiuresis studies, no fluids were given intravenously beforehand, all dogs received Ringer's solution (1 ml/min) throughout, and urinary flow rates were less than 1 ml/min.

Renal blood flow (RBF) was measured directly and indirectly. In the direct method, the left ovarian vein was ligated, and, after heparinization, the inferior vena cava (IVC) caudal to both renal veins was cannulated and ligated. The collected flow was returned via the external jugular vein. The portion of the IVC into which the renal veins drained was then cannulated and ligated cephalad to the cannula. The renal flow so collected passed to a timed volume-type flowmeter and reservoir and was also returned. Pressure in the isolated portion of the IVC did not exceed 2 mm Hg. This direct method measured the total flow from both kidneys and was used in the majority of the diuresis studies and in all of the nondiuresis studies. The indirect method (Fick principle) was used in diuresis studies only and relied on renal extraction of ^{131}I-labeled o-iodohippurate sodium (OIH) as determined by counting samples of arterial and renal venous whole blood and urine. Renal blood flow was calculated by means of the equation RBF = Uv × Ua/Aa − RVa, where Uv represents urine flow rate and Ua, Aa, and RVa represent activity concentrations (counts/min/ml) in urine, arterial blood, and renal venous blood, respectively. There was no significant, systemic difference between direct and indirect measurements of RBF (mean difference, 1.8 ± 1.5 per cent) (22 comparisons, four dogs).

Glomerular filtration rate (GFR), measured in the diuresis studies only, was based on clearance of either inulin or ^{125}I-labeled iodothalamate sodium (IOT), or both. Inulin in plasma and urine was determined by the acid-resorcinol method described by Smith.[3] The counting techniques used for simultaneous determination of OIH and IOT have been described previously.[4] GFR was calculated in the conventional manner.[2] There was no significant systematic difference between values for GFR by the two methods (mean difference, 0.3 ± 2.3 per cent) (36 comparisons, six dogs).

Renal $\dot{V}_{O_2}$ was calculated from RBF and the arterial–renal venous blood O_2 content difference. Blood O_2 content was calculated from oxyhemoglobin, hemoglobin, and P_{O_2} as described and validated previously.[5] Tubular reabsorption of sodium (TNa) was calculated by means of the equation

$$TNa = 0.95\ GFR \times PNa - Uv \times UNa$$

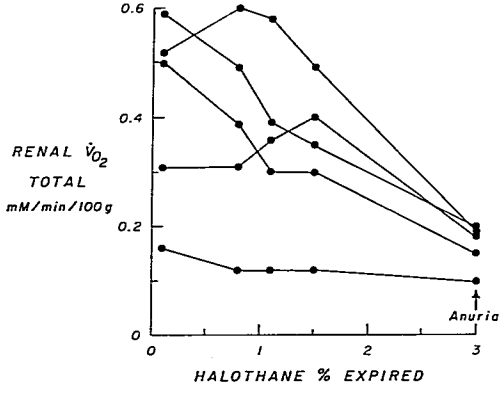

FIG. 1. Effect of halothane on renal $\dot{V}_{O_2}$ in the nondiuresis situation. As halothane was increased from 0.1 to 1.5 per cent, urinary output continued and renal $\dot{V}_{O_2}$ was little changed. At 3 per cent halothane, urinary output ceased and renal $\dot{V}_{O_2}$'s decreased to similar low values in all dogs; these were considered to represent renal basal $\dot{V}_{O_2}$.

where PNa, Uv, and UNa represent plasma sodium concentration, urine flow rate, and urine sodium concentration, respectively. Sodium concentration in plasma and urine was measured with a flame photometer using lithium as an internal standard. Osmolality of urine (U_{osm}) and plasma (P_{osm}) was measured with a Fiske osmometer, and clearances of solute (C_{osm}) and water (C_{H_2O}) were calculated by means of the two equations:

$$C_{osm} = \frac{U_{osm} \times Uv}{P_{osm}} \text{ and } C_{H_2O} = Uv - C_{osm}.$$

A negative value for C_{H_2O} indicates a net reabsorption of solute-free water.

In the diuresis studies, initial preparations required approximately two hours. When clearance techniques were to be used, priming doses of the indicators were given and a continuous infusion of a solution containing them was initiated at 1 ml/min 30 minutes prior to the first set of determinations to assure stable plasma levels. Observations were made at halothane concentrations of 0.1 and 1.0 ± 0.1 per cent, expired, with 30 minutes allowed between changes of concentration and the concentrations given initially alternated in consecutive animals. At each concentration, urine was collected during four 10-minute periods and RBF and $(A\text{-}V)_{O_2}$ were determined in triplicate before and after each collection of urine. Values obtained during unsteady states of urinary flow were discarded. Reported values are the averages of all other observations.

In the nondiuresis studies, initial preparation required approximately an hour and observations were made successively at 0.1, 0.8, 1.1, and 1.5 ± 0.1 per cent halothane, expired, and at progressively greater concentrations of halothane until anuria developed and the dog died. At each concentration, RBF and $(A\text{-}V)_{O_2}$ were determined in triplicate with 20 minutes allowed between changes in concentration. Regression equations were calculated by the method of least squares and significance was tested by Student's t test for paired data, with $P < 0.05$ being considered significant.

At necropsy, the position of the renal catheter was confirmed for the indirect studies, the total separation of renal blood was validated for the direct studies, and the right and left kidneys were removed, weighed, and ascertained to be free of gross pathologic changes.

Results

In the nondiuresis studies, renal $\dot{V}_{O_2}$ was only slightly and insignificantly decreased as halothane was increased from 0.1 to 1.5 per cent (table 1). The overall mean value for

TABLE 2. Effects of Halothane on Renal $\dot{V}_{O_2}$ and Hemodynamics during Diuresis (Ten Comparisons, Eight Dogs)

	Expired Halothane (Per Cent) (± 0.1)			
	0.1		1.0	
	Mean	SE	Mean	SE
$\dot{V}_{O_2}$ (mmoles/min/100 g)	0.60	0.03	0.50*	0.02
Renal blood flow (ml/min/100 g)	514	23	596*	36
Arterial pressure, mean (mm Hg)	136	6	103*	5
Renal vascular resistance (mm Hg/ml/min/100 g)	0.27	0.02	0.18*	0.02
Glomerular filtration rate (ml/min/100 g)	93	3	84*	4
TNa (mEq/min/100 g)	11.65	0.77	10.24*	0.82
Urine volume (ml/min)	2.40	0.38	3.66*	0.76
Urinary osmolality (mosm/l)	581	39	501*	34
Plasma osmolality (mosm/l)	287	2	288	2
C_{osm} (ml/min)	4.7	0.7	5.9	1.1
C_{H_2O} (ml/min)	−2.3	0.4	−2.2	0.4

* Significantly different ($P < 0.05$) by Student's t test for paired data.

renal $\dot{V}_{O_2}$ was 0.37 mmole or 8.3 ml/min/100 g. Actual average total kidney weight for all dogs was 90 ± 10 g, while average total body weight was 20 ± 1 kg. Accordingly, actual renal $\dot{V}_{O_2}$ was 0.37 ml/min/kg body weight, which is approximately 7 to 8 per cent of whole-body $\dot{V}_{O_2}$, as previously determined for these circumstances.[1] Renal blood flow decreased slightly but not significantly as halothane was increased despite a progressive and significant reduction in arterial blood pressure, implying a concomitant decrease in renal vascular resistance. Urinary flow was present in each dog at each halothane concentration but was decreased significantly at 1.5 per cent. There was considerable variability among dogs in actual renal $\dot{V}_{O_2}$ and the response of $\dot{V}_{O_2}$ to increases in halothane up to 1.5 per cent (fig. 1). However, when halothane was increased beyond this concentration, renal $\dot{V}_{O_2}$ decreased in each dog, and at 3 per cent halothane with a mean arterial blood pressure of 50 to 75 mm Hg, anuria was present and renal $\dot{V}_{O_2}$ values were similar in all dogs. Renal $\dot{V}_{O_2}$ in this circumstance has been termed "basal $\dot{V}_{O_2}$" since the major functions of the kidney, glomerular filtration, and tubular reabsorption and secretion are considered to have virtually ceased. In our studies, renal $\dot{V}_{O_2}$ was determined 10 to 15 times over approximately 45 minutes from the onset of anuria until just before death of the dog. Mean arterial blood pressures at these times were approximately 70 and 35 ± 5 mm Hg, respectively. Little change in renal $\dot{V}_{O_2}$ occurred during this interval, and a single average basal $\dot{V}_{O_2}$ was calculated for each dog. The mean value for basal $\dot{V}_{O_2}$ was 0.16 ± 0.02 (SE) mmole/min/100 g.

The diuresis situation provided additional information regarding the effects of halothane on renal function since the urinary output was sufficient for the use of the clearance techniques required to estimate GFR and TNa. Observed effects of 0.1 and 1.0 per cent halothane are summarized in table 2. With increase in halothane, renal $\dot{V}_{O_2}$ decreased slightly even though RBF was greater. The increase in RBF occurred despite a reduction in arterial pressure and, consequently, renal vascular resistance (RVR) decreased as halothane was increased. Despite the increase in total RBF, GFR decreased as halothane increased, presumably because of the reduction in arterial pressure. The tubular resorption rate of sodium was also decreased with increased halothane, and urinary output was greater but osmolality was less. At both halothane concentrations, urine was hyperosmolar relative to plasma and osmolar clearances were positive and similar, while H_2O clearances

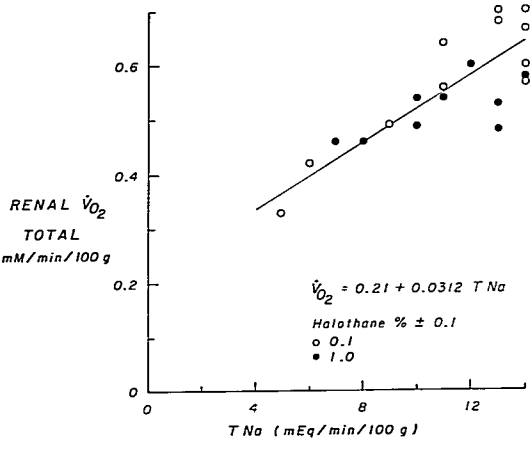

FIG. 2. Relationship of total renal V_{O_2} and tubular reabsorption of sodium (TNa) during diuresis. Total renal V_{O_2} and TNa are directly related without significant differences between 0.1 and 1.0 per cent halothane.

were negative, implying a net return to plasma of water cleared of osmotically active agents.

Renal V_{O_2} and TNa were directly related in the diuresis situation and variations in V_{O_2} among dogs were accounted for by differences in TNa (fig. 2). The regression equation relating total renal V_{O_2} (mmoles/min/100 g) and TNa (mEq/min/100 g) was

$$V_{O_2} = 0.21 + 0.0312 \pm 0.0053 \text{ TNa}.$$

Halothane concentration was not demonstrated to have a significant effect on this relationship. Reduction of these values for total renal V_{O_2} by the value for basal renal V_{O_2}, as previously determined in the nondiuresis studies (0.16 mmole/min/100 g), yielded the relationship between nonbasal V_{O_2} and TNa (fig. 3). The regression equation relating nonbasal V_{O_2} (mmoles/min/100 g) and TNa (mEq/min/100 g) was

$$V_{O_2} = 0.05 + 0.0312 \pm 0.0053 \text{ TNa}.$$

The ratios of TNa and nonbasal V_{O_2} calculated from these observations yielded a mean value of 28.3 (±0.9) equivalents of sodium reabsorbed per mole of nonbasal O_2 consumed.

Comment

The major functions of the kidney are filtration of plasma in the glomeruli and absorption and secretion of water and other substances in the tubules.[2] The quantity and composition of urine eliminated reflect the total interplay among all three activities. A more detailed evaluation of renal function is available with the aid of various indicators: inulin, which is filtered with plasma in the glomerulus but apparently neither secreted nor absorbed in the tubules, serves as an indicator of glomerular filtration rate; para-aminohippurate, being both readily filtered and actively secreted, serves as an indicator of total renal plasma flow. Comparable values, however, may be obtained more conveniently with radioiodinated iodothalamate and o-iodohippurate, respectively. The use of any of these indicators for determination of GFR or RBF requires conditions appropriate to the application of the Fick formula, including steady levels of the substance in blood entering and leaving the kidney and in urine eliminated and steady flow rates of blood and urine. Furthermore, the flow of urine must be sufficient to clear enough of the substance for analysis and to lessen the discrepancies in composition between urine collected and urine currently being formed. These conditions usually are approached by inducing and maintaining diuresis with intravenous administration of solutions which result in steady urinary flow rates of at least 2

ml/min. Thus, effects of drugs evaluated by application of clearance techniques must be considered in the light of the conditions arranged to carry out the measurements. This becomes particularly cogent in studies of halothane, since vigorous measures must be employed to overcome the extreme antidiuresis associated with the use of halothane.[6]

In view of the foregoing, our experiments were designed to include observations obtained by direct methods in nondiuresis situations, by clearance methods in diuresis situations, and by both methods in some diuresis situations. The direct methods provided the information most relevant to our interest regarding the effects of halothane on renal $\dot{V}_{O_2}$ in the circumstances previously studied and, additionally, the means to determine renal basal $\dot{V}_{O_2}$, while the clearance methods made possible examination of the effects of halothane on glomerular filtration rates and the relationship between tubular reabsorption of sodium and nonbasal renal $\dot{V}_{O_2}$.

In previous studies, whole-body, myocardial, cerebral, and skeletal muscle $\dot{V}_{O_2}$ decreased as halothane was increased from 0.1 to 1.5 per cent.[1, 7, 8] In this study, renal $\dot{V}_{O_2}$ was approximately 7 to 8 per cent of whole-body $\dot{V}_{O_2}$ but did not change significantly over this range of halothane concentrations. Renal $\dot{V}_{O_2}$ decreased only after the increase in halothane produced a reduction in arterial pressure sufficient to lead to a decrease in glomerular filtration rate. With further increases in halothane, glomerular filtration ceased, anuria was present, and renal $\dot{V}_{O_2}$'s were low and similar in all dogs. These findings are compatible with current concepts regarding factors contributing to renal $\dot{V}_{O_2}$.

While it had long been recognized that renal $\dot{V}_{O_2}$ roughly paralleled renal blood flow and glomerular filtration rate, it remained for Hess Thaysen and associates[9] and Kramer and Deetjen[10] to demonstrate independently that total renal $\dot{V}_{O_2}$ consisted of a basal component, occurring during anuria, and a nonbasal component, directly proportional to filtration rate and to net tubular reabsorption of sodium. The basal component apparently is involved in maintenance of cellular structure and in returning sodium that leaks into the tubular cells over the blood side of the membrane, and has been estimated to amount to approximately 0.1 mmole/min/100 g.[11] The nonbasal component has been shown to have a direct relationship to the amount of sodium reabsorbed under various experimental conditions, with a value of approximately 28 sodium equivalents per mole of nonbasal O_2 consumed.[11, 12] Similar values for basal $\dot{V}_{O_2}$ and the ratio of sodium reabsorbed to nonbasal $\dot{V}_{O_2}$ were found for halothane anesthesia in the present study. It is our interpretation that the lack of change in total renal $\dot{V}_{O_2}$ as halothane was increased to 1.5 per cent is a reflection of the relative steady rates of glo-

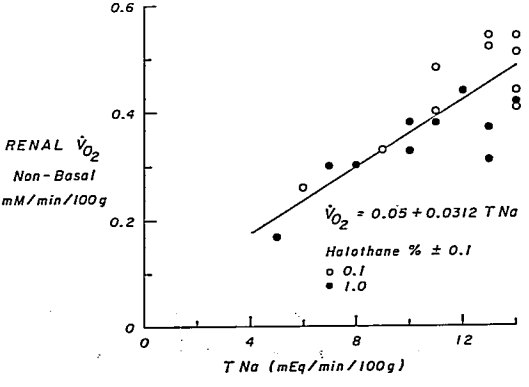

FIG. 3. Relationship of nonbasal renal $\dot{V}_{O_2}$ (total–basal) and tubular reabsorption of sodium (TNa) during diuresis. Nonbasal renal $\dot{V}_{O_2}$ and TNa are directly related.

merular filtration and tubular reabsorption of sodium under these conditions. Maintenance of the latter in the presence of a progressive decrease in arterial pressure must, in some part, be attributed to reduction in renal vascular resistance and preservation of total renal blood flow rates.

The findings of the present study confirm and, in ways previously discussed, augment those of Deutsch and associates,[6] who determined the effects of halothane on renal function in normal man. These investigators were necessarily limited, as were we to some extent, to the use of indirect clearance methods for measurement of renal function, which necessitated the administration of acute and maintaining water loads sufficient to result in a satisfactory urinary output. As they and we found, this is particularly difficult during halothane anesthesia due to an associated antidiuretic response which results in elimination of small volumes of hyperosmolar urine and osmolar clearances that are positive and water clearances that are negative. The basis for the occurrence of this with halothane has not been established but may include, as Deutsch and co-workers[6] infer, the release of antidiuretic hormone.

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Drugs

PANCURONIUM Pancuronium bromide, first synthesized in 1964 by C. L. Hewitt and D. S. Savage, is a bisquaternary amino steroid. Buckett and Bonta, in 1966, demonstrated its neuromuscular blocking properties in animals. In 1967, Baird and Reid, in a pilot study, showed that in man the drug produced a nondepolarizing neuromuscular block with a potency five times that of tubocurarine. The durations of action of the two drugs appeared to be similar. Experience with pancuronium suggests that it is a useful nondepolarizing myoneural blocker with few side-effects. The absence of adverse cardiovascular effects makes the drug particularly valuable for poor-risk patients. Unfortunately, however, this fact has perhaps led some anesthetists into giving larger doses of pancuronium than are necessary. It would seem that the potency of this drug relative to tubocurarine may increase with increasing dosage, and that in the normally accepted dose range, pancuronium is five to six times as potent as tubocurarine. (*Baird, W. L. M.: Clinical Experience with Pancuronium, Proc. Roy. Soc. Med. 63: 697 (July) 1970.*)