

## Renovascular Hypertension: Effect of Halothane and Enflurane

Jack R. Woodside, Jr., M.D.,\* Judy J. Beckman, B.S.,† John S. Althaus, M.S.,† Michael J. Peach, Ph.D.,‡  
David E. Longnecker, M.D.,§ Edward D. Miller, Jr., M.D.§

Male Wistar rats were anesthetized at 6 weeks of age and a silver clip placed around the renal artery to produce renovascular hypertension. The rats were allowed to grow on a normal sodium diet for the next 6-9 weeks. Using diethyl ether anesthesia, arterial and venous cannulae were placed and the animals allowed to awaken in restraining cages. The group of rats was divided into three groups: awake (n = 7), halothane 1.3 vol% (n = 9), and enflurane 2.2 vol% (n = 8). The protocol consisted of a 1-h control awake period, 1 h of stable anesthesia (one group received no anesthesia), and 30-min iv infusion of saralasin, a competitive inhibitor of angiotensin II. Plasma renin activity (PRA) and plasma catecholamines were measured after 1 h of stable anesthesia and after the saralasin infusion. In additional rats treated identically, radiolabelled microspheres were used to measure cardiac output and regional blood flows during halothane (n = 7) or enflurane (n = 6) anesthesia.

Principal responses were as follows: mean arterial pressure (MAP) was  $193 \pm 4$  mmHg awake and decreased to  $114 \pm 3$  mmHg and  $135 \pm 3$  mmHg with halothane and enflurane, respectively. Saralasin decreased MAP in the awake group to  $176 \pm 3$  mmHg and to  $69 \pm 3$  mmHg and  $96 \pm 5$  mmHg with halothane and enflurane, respectively. PRA in the awake rats was  $7.24 \pm 1.3$  ng · ml<sup>-1</sup> · h<sup>-1</sup>. PRA increased with halothane but decreased with enflurane. Plasma catecholamines were decreased markedly by saralasin and by both anesthetic agents. Cardiac output was normal in awake rats and blood pressure elevation was due to increased peripheral resistance. Both anesthetic agents decreased cardiac output and myocardial blood flow and increased brain blood flow. The authors conclude that the cardiovascular and hormonal responses to halothane and enflurane anesthesia in renovascular hypertensive rats are different than the responses seen in normotensive rats. Such alterations may explain the differences seen in regional blood flow to various organs. (Key words: Anesthetics, volatile: enflurane, halothane. Hypertension: renovascular. Polypeptides: renin-angiotensin. Polypeptides: antagonists, saralasin. Sympathetic nervous system: catecholamines.)

ANESTHESIOLOGISTS often attempt to control arterial pressure carefully during anesthesia and operation using potent inhalational agents. Hypertensive patients are at increased risk for strokes and myocardial infarction, and the value of long-term blood pressure control is established.<sup>1-3</sup> Whether acute reductions in blood pressure by potent inhalational anesthetic agents have similar beneficial effects or whether such interventions might be del-

eterious has not been determined, however. In untreated hypertensive patients, Prys-Roberts and colleagues found an increased incidence of myocardial ischemia in patients anesthetized with halothane.<sup>4</sup> Subsequently, he showed no deleterious effects of Althesin®, fentanyl, and nitrous oxide anesthesia in patients with severe renovascular hypertension who were receiving antihypertensive therapy.<sup>5</sup> Goldman and Caldera suggested that "special care should be taken when halothane is added to nitrous oxide in anesthetizing patients who have a history of hypertension."<sup>6</sup> Such reports suggest that potent anesthetic agents might be harmful to patients, whereas a technique that tended to support blood pressure might be more beneficial in the hypertensive subject. Presumably, the risks of acute reduction of arterial pressure are those of organ perfusion and tissue viability.

The present study examined the influences of halothane or enflurane anesthesia in rats with arterial hypertension created by clipping a renal artery. This model produces hypertension through the renin-angiotensin system and has been well characterized by many investigators.<sup>7,8</sup> The model accurately reflects changes known to occur in humans with renovascular hypertension.<sup>9</sup> Although renovascular hypertension represents only 5% of all hypertensive subjects, the hemodynamic patterns of renovascular hypertension are similar to those in patients with essential hypertension, *i.e.*, increased total peripheral resistance with normal cardiac output.

The present investigations examined more than just the blood pressure responses to two clinically used anesthetics. Hemodynamic data were obtained in rats given radioactive microspheres in order to determine cardiac output, total peripheral resistance, and the influence of these two anesthetics on the distribution of blood flow to vital organs in hypertensive animals. Sympathetic nervous system activity was estimated by measurement of circulating catecholamines, and the role of the renin-angiotensin system was assessed by plasma renin activity (PRA) and the response to the specific competitive inhibitor of angiotensin II, saralasin, since these systems are involved intimately in blood pressure control during hypertension. Such data, which can only be obtained in experimental animals, should allow a more rational determination of anesthetic choice for the hypertensive patient.

### Methods

Male Wistar rats (150 g; 6 weeks of age) were anesthetized with ether; the left kidney was exposed through

\* Fellow in Anesthesiology.

† Research Assistant.

‡ Professor of Pharmacology.

§ Professor of Anesthesiology.

Received from the Department of Anesthesiology, University of Virginia Medical School, Charlottesville, Virginia 22908. Accepted for publication November 4, 1983. Supported in part by grants from the National Institutes of Health GM-24313, HL 26370, Research Career Development Award GM-00457 (EDM), and Training Grant T-32GM07590. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, 1981.

Address reprint requests to Dr. Miller.

a flank incision; and a 0.1 mm silver clip was placed on the renal artery. The other kidney was left undisturbed. The incision was closed, and the blood pressure was determined weekly thereafter by the tail-cuff method (Narco Biosystems, Inc.). At 12–15 weeks of age, animals with a systolic pressure greater than 180 mmHg (normal approximately 150 mmHg) were selected for further studies.

Twenty-four rats were anesthetized briefly with diethyl ether delivered via a nose cone, and a femoral artery and vein were cannulated (PE-50 tubing). The cannulae were exteriorized and flushed with a solution of heparin and physiologic saline. The rats were placed in restraining cages (Braintree Scientific Inc.) for at least 1 h in order to allow recovery from anesthesia. Blood pressure, which was monitored continuously through the arterial cannula by a Statham P23Db<sup>®</sup> pressure transducer using a Brush Mark 2400<sup>®</sup> recorder, had stabilized well before the end of the recovery period, and the animals were awake and alert. The protocol consisted of a 1-h awake period, a 20-min anesthetic induction period, 60 min of anesthesia, and a 30-min infusion of saralasin. Anesthesia was established with either halothane 1.3 vol% (n = 9) or enflurane 2.2 vol% (n = 8). These values represent approximately equipotent anesthetic concentrations in young rats.<sup>10,11</sup> A control group (n = 7) was treated identically but remained unanesthetized throughout. All animals breathed room air spontaneously throughout the experiment. Inhaled concentrations of the volatile agents were determined at 15-min intervals by gas chromatography.<sup>†</sup> All animals were placed under a heating lamp to maintain rectal temperature at 37° C.

In order to ensure a large excess of saralasin relative to angiotensin II at the angiotensin-binding sites, an initial dose of saralasin, 100 µg/kg, dissolved in 0.9% saline solution (approximately 150 µg/ml), was infused intravenously, and the infusion was maintained at 10 µg · kg<sup>-1</sup> · min<sup>-1</sup> for the next 30 min.<sup>12</sup> The volume of saralasin administered did not exceed 0.8 ml.

Arterial blood (0.5 ml) for determination of PRA was obtained immediately prior to anesthesia. After 1 h of stable anesthesia, 1.5 ml of blood was obtained for determination of PRA and plasma catecholamines. A third arterial blood sample was obtained at the end of the infusion for determination of PRA, plasma catecholamines, and arterial blood gases. The removed blood, placed in a vial containing EDTA, was centrifuged, the plasma was withdrawn, and the red blood cells were suspended in an equal volume of saline solution and were administered intravenously to replace the shed blood. Catheters were flushed periodically with normal saline to ensure accurate blood pressure measurements. Plasma renin activity was

estimated using 0.2 ml plasma instead of 1 ml plasma, as is described by Haber *et al.*,<sup>13</sup> using New England Nuclear reagents. The plasma was incubated for 2 h to generate angiotensin I, which was estimated by radioimmunoassay and the renin activity calculated as ng · ml<sup>-1</sup> · h<sup>-1</sup>. The plasma samples from the three groups were assayed randomly in 10 separate renin assays. Standard curves for each assay were done in triplicate, and all samples were assayed in duplicate. Renin values that exceeded the standard curve values were diluted and reassayed.

Blood samples for analysis of catecholamines were collected in iced polystyrene tubes containing EDTA. After centrifugation, 500 µl of plasma was collected and stored at -80° C for later analysis. Catecholamines were extracted 1–10 days later and then assayed by high-performance liquid chromatography. Briefly, 8 pmol of internal standard (3,4-dihydroxybenzylamine) were added to 500 µl plasma and the catecholamines were absorbed to alumina under alkaline conditions. The catecholamines then were eluted with 250 µl of 0.1 N perchloric acid. Thereafter, 200 µl of the eluate was injected into the chromatograph and separated by an ODS 5-µm reverse phase column. Catecholamines were detected electrochemically with a 30-pg sensitivity threshold.<sup>14</sup> There was less than a 5% error in repeated determinations of samples containing 100–200 pg/ml of catecholamines.

In order to assess the influence of anesthetic agents on cardiac output and distribution of blood flow, 13 additional Wistar rats (10–12 weeks of age) with renovascular hypertension were studied. The rats were anesthetized with diethyl ether, and PE 50 polyethylene tubing was passed through the right carotid artery and into the left ventricle using pressure monitoring to verify location. The neck incision was closed, and a femoral artery was cannulated with PE 50 tubing. Both catheters were tunneled subcutaneously through the skin over the back and flushed with a solution of heparin and physiologic saline solution. The rats then were placed in restraining cages and allowed to awaken. Blood pressure was monitored as described previously.

The protocol consisted of a 1-h awake period, a 20-min induction period, and a 1-h period of stable anesthesia. Anesthesia was established with either halothane 1.3 vol% (n = 7) or enflurane 2.2 vol% (n = 6) to determine cardiac output and distribution of blood flow.<sup>15</sup> Carbonized microspheres were injected.<sup>13</sup> Strontium-85 (<sup>85</sup>Sr) or cerium-141 (<sup>141</sup>Ce) labelled microspheres (15 ± 1.1 µm) with specific activities of 9.6 mCi/g for <sup>85</sup>Sr and 12.8 mCi/g for <sup>141</sup>Ce were used. These were suspended in dextran, 10%, containing Tween 80, 0.05%, and counted in a gamma counter (Beckman Biogamma<sup>®</sup>, Irvine, California) at the appropriate energy spectrum of each isotope. After initial counting, the microspheres were agitated again, and 0.1–0.2 ml (40,000–60,000 micro-

<sup>†</sup> Gow-MAC Model 750 Flame Ionization Detector; 1.83 meters SS column containing 20% SE30 on Chromasorb W.

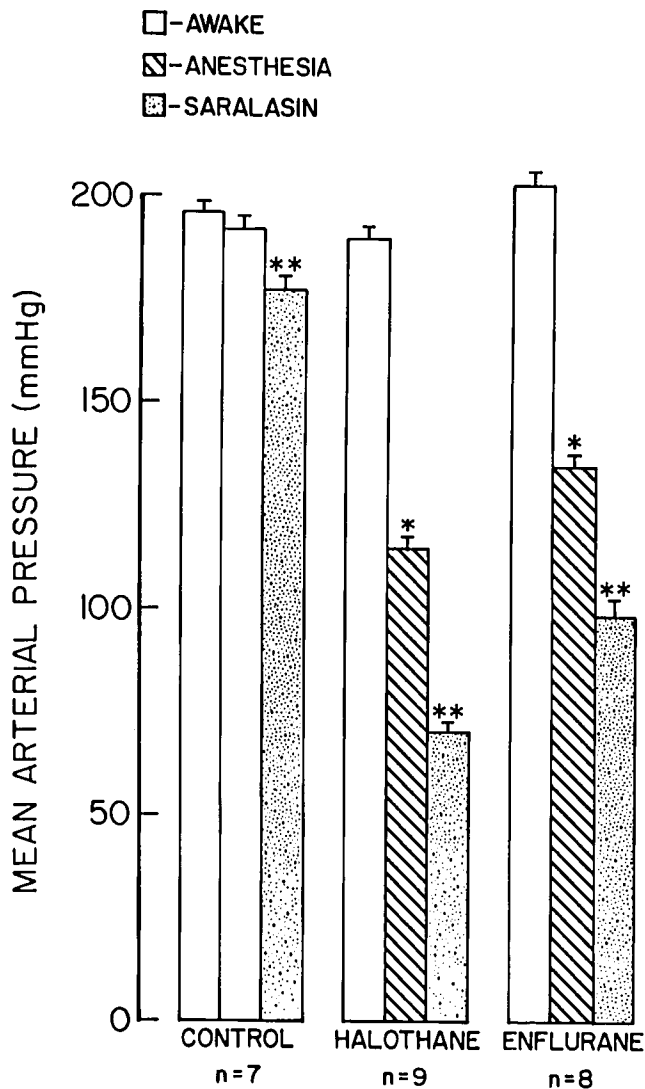


FIG. 1. Mean arterial pressure (mmHg) in rats with renovascular hypertension. Mean arterial pressure decreased significantly ( $*P < 0.05$ ) in rats anesthetized with halothane (1.3 vol%) or enflurane (2.2 vol%). With the infusion of saralasin, a further significant ( $**P < 0.05$ ) decrease in mean arterial pressure was observed in all three groups.

spheres) were injected into the left ventricular catheter over 2 s and the catheter was flushed with saline solution 0.4 ml. Blood was withdrawn from the femoral artery by a constant withdrawal pump for 10 s prior to and 60 s after the microsphere injection. The blood then was placed in a preweighed counting vial and the actual withdrawal rate (approximately 0.76 ml/min) was determined by weighing the vial. The empty injection syringe again was counted to determine any residual microspheres not injected. The above procedure was repeated for each isotope. Microspheres were injected at the end of the awake control period ( $^{85}\text{Sr}$ ) and after 1 h of stable anesthesia ( $^{141}\text{Ce}$ ). Then the animals were killed by injection

of potassium chloride through the ventricular catheter and the organs were removed, weighed, and placed in counting vials. The position of the left ventricular catheter was verified by direct vision. Samples of skin, muscle, liver, and small intestine were taken; otherwise, the whole organ was counted. Total weights of the liver and small intestine were determined for each animal. Tissue and blood samples then were counted for 5 min in a gamma counter at the appropriate energy spectrum, allowing for overlap of strontium in the cerium window.

Cardiac output was determined by the reference sample method (cardiac output = counts injected  $\times$  reference sample withdrawal rate  $\div$  reference blood counts). Regional distribution of cardiac output was calculated by comparing the radioactivity in each organ with the total injected radioactivity. Organ flow was determined by multiplying the cardiac output by the fractional distribution of the cardiac output to the organ.

Previous work from our laboratory reported hemodynamic and renin responses to halothane and enflurane anesthesia in normotensive Wistar rats, and these values were used for comparison to the results obtained here.<sup>16,17</sup> However, these reports did not include measurements of plasma catecholamines, since this is a technique developed recently in our laboratory. Therefore, normotensive Wistar rats ( $n = 10$ ) were cannulated as described previously and allowed to awaken. Blood for plasma catecholamine analysis was obtained at the end of 1 and 2 h and again after a 30-min infusion of saralasin for comparison with similar samples from the animals with renovascular hypertension.

Data are presented as the mean values  $\pm$  the standard error of the mean. Statistical significance was determined by one-way analysis of variance, Student's  $t$  test for paired or unpaired data, or analysis of covariance.  $P < 0.05$  was considered significant.

## Results

Significant arterial hypertension (mean arterial pressure  $193 \pm 4$  mmHg) with increased plasma renin activity ( $7.24 \pm 1.3$  ng  $\cdot$  ml $^{-1}$   $\cdot$  h $^{-1}$ ) was present during the awake period. Recent data from our laboratory reported that mean arterial pressure for 30 normal awake Wistar rats was  $124 \pm 1$  mmHg and a plasma renin activity was  $2.59 \pm 0.21$  ng  $\cdot$  ml $^{-1}$   $\cdot$  h $^{-1}$ .<sup>18</sup>

The induction and maintenance of stable anesthesia resulted in dramatic but similar decreases in mean arterial blood pressure in rats anesthetized with halothane or enflurane (fig. 1). Mean arterial pressure did not change during the comparable interval in awake rats.

Plasma renin activity increased significantly in rats anesthetized with halothane but showed a small but significant decrease in rats anesthetized with enflurane.

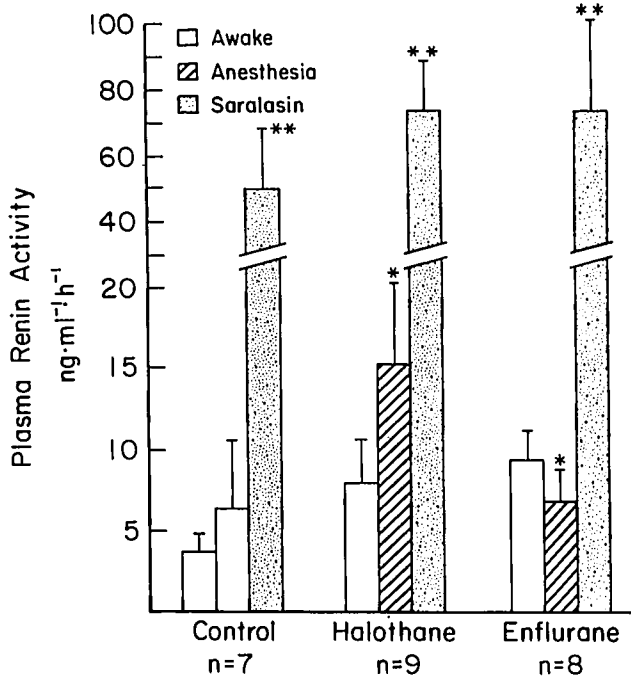


FIG. 2. Plasma renin activity ( $\text{ng} \cdot \text{ml}^{-1} \cdot \text{h}^{-1}$ ) in rats with renovascular hypertension. A significant increase ( $*P < 0.05$ ) was observed in rats anesthetized with halothane (1.3 vol%), but a significant decrease was observed in rats anesthetized with enflurane (2.2 vol%). With the infusion of saralasin, all groups demonstrated significant ( $**P < 0.05$ ) increases in plasma renin activity.

Awake rats showed no alteration in plasma renin activity (fig. 2).

The infusion of saralasin resulted in a decrease in mean arterial pressure (MAP) in all groups (fig. 1). The average decrease was  $16 \pm 4$  mmHg in awake animals, while MAP decreased  $45 \pm 5$  and  $39 \pm 10$  mmHg in those receiving halothane or enflurane, respectively. Plasma renin activity was significantly increased in all groups after the saralasin infusion (fig. 2).

Arterial blood gas analysis, which was performed only after saralasin infusion in order to minimize blood sampling during the experiments, demonstrated normal acid-base balance in awake rats and those anesthetized with enflurane.  $\text{PaCO}_2$  was increased in animals breathing halothane and enflurane as compared with awake rats but still was within the physiologic range. Arterial oxygen

TABLE 1. Arterial Blood Gases

	$\text{Po}_2$ mmHg	$\text{Pco}_2$ mmHg	pH
Awake (n = 7)	$76 \pm 4$	$34 \pm 4$	$7.45 \pm 0.06$
Halothane (n = 9)	$59 \pm 3^*$	$40 \pm 2$	$7.35 \pm 0.02^*$
Enflurane (n = 8)	$72 \pm 5$	$42 \pm 3$	$7.37 \pm 0.03$

\*  $P < 0.05$  when compared with awake control.

TABLE 2. Plasma Catecholamines in Awake Normotensive Wistar Rats (n = 10)

	Norepinephrine (pg/ml)	Epinephrine (pg/ml)
1 h restrained	$244 \pm 36$	$164 \pm 42$
2 h restrained	$166 \pm 23$	$141 \pm 40$
+1/2 h saralasin	$195 \pm 49$	$154 \pm 34$

tension was  $59 \pm 3$  mmHg in rats anesthetized with halothane, while more usual conditions existed in the animals awake or anesthetized with enflurane (table 1).

Plasma catecholamines were unchanged in the 10 normal restrained Wistar rats after 1 and 2 h awake and after 1/2 h of saralasin (table 2).

Plasma catecholamines in awake rats with renovascular hypertension were increased as compared with those in normotensive rats. While the infusion of saralasin in normal Wistar rats did not alter plasma catecholamines, a similar infusion in the awake rats with renovascular hypertension resulted in marked decreases in plasma norepinephrine and epinephrine (table 3).

Plasma norepinephrine and epinephrine concentrations were significantly less in renovascular hypertensive rats anesthetized with halothane or enflurane, as compared with awake hypertensive rats. Norepinephrine and epinephrine values in the anesthetized rats were similar to those in awake, normotensive rats. The infusion of saralasin in the anesthetized hypertensive rats did not result in changes in plasma catecholamines.

The microsphere protocol supplied additional hemodynamic data in the rats that were anesthetized with halothane or enflurane. While awake, the mean arterial pressure was  $172 \pm 4$  mmHg (table 4) and cardiac output was  $143 \pm 6$  ml/min in these 300–400 g rats. With the induction and maintenance of halothane or enflurane anesthesia, blood pressure decreased to  $118 \pm 9$  mmHg or  $125 \pm 6$  mmHg, respectively, values that were similar to those in the anesthetized rats described previously. These decreases in blood pressure were due to decreases in cardiac output, since there was a tendency for total peripheral resistance to increase in both groups (although

TABLE 3. Plasma Catecholamines in Renovascular Hypertensive Rats

	Norepinephrine (pg/ml)	Epinephrine (pg/ml)
Awake (n = 7)	$1330 \pm 140$	$1240 \pm 63$
+ saralasin	$560 \pm 110^*$	$510 \pm 69^*$
Halothane (n = 9)	$220 \pm 28^\dagger$	$450 \pm 32^\dagger$
+ saralasin	$330 \pm 50$	$460 \pm 113$
Enflurane (n = 8)	$220 \pm 30^\dagger$	$390 \pm 53^\dagger$
+ saralasin	$190 \pm 30$	$250 \pm 64$

\*  $P < 0.05$  comparing awake with awake plus saralasin infusion.

†  $P < 0.05$  comparing awake with agent only.

TABLE 4. Hemodynamic Responses to Halothane and Enflurane in Renovascular Hypertensive Rats

	Awake (n = 13)	Halothane (n = 7)	Enflurane (n = 6)
Mean blood pressure (mmHg)	172 ± 4	118 ± 9*	125 ± 6*
Heart rate (beats/min)	420 ± 10	348 ± 10*	324 ± 12*
Cardiac output (ml/min)	143 ± 6	99 ± 11*	94 ± 7*
Total peripheral resistance mmHg · ml <sup>-1</sup> · min	1.21 ± 0.06	1.65 ± 0.14*	1.38 ± 0.15
Stroke volume (ml)	0.33 ± 0.01	0.29 ± 0.03*	0.29 ± 0.03*

\*  $P < 0.05$  compared with awake.

this was significant only in rats anesthetized with halothane).

Individual organ blood flows were altered by halothane and enflurane (fig. 3). Brain blood flow increased with halothane or enflurane anesthesia because of a decrease in vascular resistance. Halothane and enflurane anesthesia decreased cerebral vascular resistance markedly to  $119 \pm 23$  and  $102 \pm 19$ , respectively, from the awake value of  $217 \pm 18$  mmHg · ml<sup>-1</sup> · min · g.

Coronary blood flow per gram of tissue was decreased in the anesthetized rats. Heart weight for the renovascular hypertensive rats was  $1.74 \pm 0.20$  g, which is significantly greater than the  $1.08 \pm 0.14$  g for normal hearts.<sup>13</sup> Renal blood flow was unaltered by halothane or enflurane. Renal mass was  $1.39 \pm 0.24$  g for the left kidney and  $2.24 \pm 0.40$  g for the right, so that there was a relative decrease in blood flow to the left kidney which had been clipped. There was a tendency for blood flow to decrease in skin, muscle, stomach, and intestine, but these reached statistical significance only in the skin of rats anesthetized with enflurane.

### Discussion

The present experiments examined the effects of halothane or enflurane anesthesia on one model of exper-

imental hypertension: the two-kidney, one-clip Goldblatt model. Arterial hypertension developed shortly after renal artery clipping in these animals. The initial increase in blood pressure in this model results from release of renin and the subsequent formation of angiotensin II.<sup>19</sup> This type of hypertension is reversed by inhibitors of the renin-angiotensin system for several weeks. Eventually other factors, including aldosterone, appear to play a more important role in maintenance of hypertension, and plasma renin activity returns toward control levels.<sup>20</sup>

The hypertensive rats studied all had increased plasma renin activity, plasma catecholamines, and arterial pressure while awake. When saralasin, the competitive inhibitor of angiotensin II, was infused, mean arterial pressure and plasma catecholamines decreased. Plasma renin activity increased dramatically when the normal negative feedback control of angiotensin II on renin release was abolished by saralasin.<sup>21</sup>

The probable cause of the decrease in plasma catecholamines in the awake period related to the saralasin infusion, since angiotensin II is known to facilitate norepinephrine release from sympathetic nerve terminals.<sup>22</sup> Presumably, the blockade of the action of angiotensin II by saralasin also blocked the facilitated release of catecholamine, and plasma levels of these substances decreased. That sympathetic nervous system activity is an

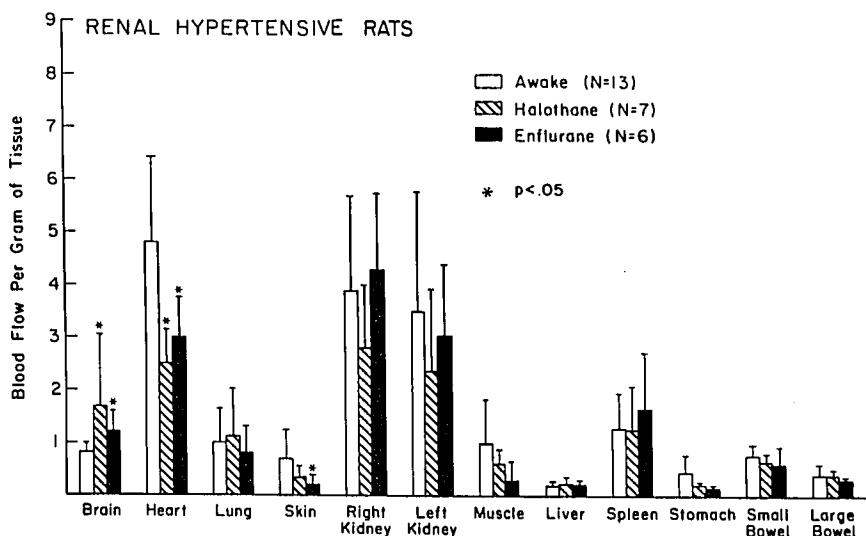


FIG. 3. Blood flow per gram of tissue (ml · min<sup>-1</sup> · g<sup>-1</sup>) in rats with renovascular hypertension, obtained with the use of the radioactive microsphere technique. Significant increases in brain blood flow were seen in rats anesthetized with halothane (1.3 vol%) and enflurane (2.2 vol%). Decreases in blood flow to myocardium were seen with both anesthetic agents. A significant decrease in blood flow to skin was seen only in animals anesthetized with enflurane.

important component of the development of renovascular hypertension is borne out by the experiments of Antonaccio and co-workers.<sup>23</sup> They showed that an intact sympathetic nervous system was necessary for the full development of renovascular hypertension in rats.

The model of hypertension chosen here is hemodynamically similar to that which is known to occur in humans. Total peripheral resistance is increased and cardiac output is normal in human essential hypertension.<sup>24</sup> Previous work in normal awake rats from our laboratory<sup>15</sup> revealed the cardiac output to be similar to what we now report in hypertensive rats. In that previous publication, we showed that the blood pressure decrease during halothane was due to a decrease in cardiac output, while that in rats anesthetized with enflurane was due to a decrease in total peripheral resistance. In the present study, halothane caused an increase in peripheral resistance, while enflurane resulted in no change in peripheral resistance. Both agents markedly decreased cardiac output in the hypertensive rats. This may be due to the effect of halothane and enflurane on the performance of the hypertrophied left ventricle. No other measurements of left ventricular function were done, and the influence of these anesthetics on this model cannot be predicted.

The infusion of saralasin resulted in dramatic decreases in blood pressure in the anesthetized rats. While we did not measure angiotensin II directly, most studies have shown a good correlation between plasma renin activity and angiotensin II in intact animals.<sup>25</sup> Why the initial plasma renin activity did not predict different responses to saralasin was not evident from this study. In the present study, the increase in PRA with halothane anesthesia and the decrease in PRA with enflurane anesthesia may reflect differences in the pressure drop across the renal artery stenosis caused by the two agents. Since we did not measure distal renal artery pressure, this supposition remains unproven. Our previous work showed that, in normal rats anesthetized with halothane or enflurane, plasma renin activity was not a good indicator of the action of the renin-angiotensin system on blood pressure support during anesthesia.<sup>16</sup> Even though PRA increased with one agent and decreased with the other, the response to saralasin was depressor in both. Vascular reactivity during anesthesia is altered, and this may explain the lack of correlation between plasma renin activity and a saralasin responsiveness, but we have no direct evidence to either support or refute this hypothesis.<sup>26</sup> However, other sites of angiotensin II production are known to exist, and the renin activity in plasma does not measure the renin at these sites. For example, all the components of the renin-angiotensin system have been found in the brain and especially in the walls of blood vessels and renin activity at these sites could affect peripheral vascular control even without changes in plasma renin activity.<sup>27,28</sup>

Relative hypoxia was seen in the animals receiving halothane anesthesia. Previous reports from our laboratories have demonstrated normal arterial oxygenation in normotensive rats receiving inhalation anesthetics.<sup>15,29,30</sup> In these previous reports, halothane tended to have lower arterial oxygen than did animals anesthetized with enflurane, and this may be accentuated in these hypertensive rats. Furthermore, arterial blood gases were sampled only at the end of the saralasin infusion when arterial pressure was reduced markedly especially in those receiving halothane. The reduction in arterial pressure likely contributed to ventilation perfusion abnormalities that were manifested by arterial hypoxemia. Whether hypoxia was present throughout the protocol cannot be ruled out, although our previous reports could suggest that this was unlikely.

Plasma catecholamines in these renovascular hypertensive animals were increased in the awake state. It is unlikely that these values were increased due to restraint, because values in our normotensive awake rats maintained in similar cages were similar to those found in chronically instrumented, unrestrained, awake rats.<sup>31</sup> Whether these renal hypertensive rats are more susceptible to the stress of immobilization because of their previous surgery at 6 weeks was not addressed in these studies. That halothane is able to decrease previously increased plasma catecholamines has been demonstrated by the experiments of Roizen and co-workers.<sup>32</sup> Whether halothane can further decrease normal plasma catecholamines has been disputed, however.<sup>33</sup> A further decrease in plasma catecholamines was not seen during saralasin in anesthetized animals but was observed in the awake rats. This could suggest that the facilitative release of catecholamines occurs only at increased blood concentrations of angiotensin II. On the other hand, the dramatic decrease in blood pressure may activate the sympathetic nervous system and offset any potential decline in plasma catecholamines due to blockade of the renin-angiotensin system. Which mechanism is operative in this setting is unknown.

The microsphere data suggested that blood flow to most organs remained intact during anesthesia, despite reductions in arterial pressure. The increased brain flow might be due to either the direct vascular effects of the anesthetics or the accompanying slight increase in PaCO<sub>2</sub>. In the awake state, slight hypocarbia existed and, therefore, any small elevation in PaCO<sub>2</sub> would result in increased brain blood flow. Certainly, in this hypertensive model brain flow is preserved despite a large decrease in blood pressure, and the cerebral vasculature appeared to respond as expected to changes in PaCO<sub>2</sub> and/or potent anesthetic agents (*i.e.*, decreased cerebrovascular resistance).

Myocardial blood flow did decrease, but this probably reflects the decreased myocardial oxygen demand of the

TABLE 5. Comparison of Tissue Blood Flow ( $\text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$ ) for Normotensive and Hypertensive Rats during the Anesthetic Period

	Halothane		Enflurane	
	Normotensive (n = 6)	Hypertensive (n = 7)	Normotensive (n = 6)	Hypertensive (n = 6)
Brain	1.66 ± 0.25	1.72 ± 0.56	1.14 ± 0.30	1.23 ± 0.17
Heart	4.29 ± 0.81	2.48 ± 0.29*	4.62 ± 0.90	3.05 ± 0.34
Lung	1.48 ± 0.19	1.09 ± 0.38	1.39 ± 0.19	0.79 ± 0.25
Skin	0.11 ± 0.01	0.37 ± 0.09*	0.08 ± 0.01	0.19 ± 0.09
(R) Kidney	4.72 ± 0.44	2.82 ± 0.49*	5.37 ± 0.58	4.31 ± 0.64
(L) Kidney	4.89 ± 0.40	2.35 ± 0.65*	5.22 ± 0.94	3.07 ± 0.58
Muscle	0.24 ± 0.13	0.64 ± 0.11*	0.12 ± 0.02	0.29 ± 0.17
Liver	0.34 ± 0.06	0.25 ± 0.05	0.43 ± 0.05	0.23 ± 0.04*
Spleen	0.97 ± 0.11	1.28 ± 0.34	1.81 ± 0.46	1.65 ± 0.48
Stomach	0.37 ± 0.05	0.21 ± 0.03*	0.39 ± 0.05	0.17 ± 0.03*
Small intestine	1.32 ± 0.10	0.66 ± 0.06*	1.20 ± 0.18	0.60 ± 0.15*
Large intestine	0.51 ± 0.07	0.40 ± 0.05	0.54 ± 0.04	0.28 ± 0.03*
Total flow (ml/min)	100 ± 13	99 ± 11	126 ± 7	94 ± 7*

\*  $P < 0.05$ , comparing normotensive to hypertensive for each anesthetic. The normotensive data have been reported previously.<sup>13</sup>

heart, since cardiac output and blood pressure also decreased. In these hypertrophied ventricles, this decrease in blood flow was greater in animals anesthetized with halothane than enflurane. Other organs showed minimal flow alterations during halothane or enflurane anesthesia, suggesting that these agents had little effect on tissue blood flow. However, such comparisons to the awake hypertensive state do not reflect the influences of hypertension alone on regional circulation. Table 5 is a comparison of our previous data for blood flow to various organs in normotensive animals<sup>15</sup> with those obtained here in hypertensive rats. Relative to the normotensive animal, there were marked decreases in blood flow to heart, kidney, stomach, and small intestine in hypertensive rats anesthetized with halothane. This is substantiated further by the significant increase in total peripheral resistance in these hypertensive rats anesthetized with halothane (table 4). In contrast, skin and muscle flows were increased in hypertensive rats receiving halothane. This may represent inappropriate redistribution of blood flow to nonvital organs. However, the measurement technique used here employed only aliquots of skin and muscle, and larger samples of these organs would be required to document this redistribution of flow with certainty.

Enflurane had less of an effect on individual organ flow in hypertensive rats than did halothane anesthesia. While cardiac output was decreased significantly in hypertensive rats anesthetized with enflurane, there were significant changes in flow only to liver, stomach, small and large intestine when compared with those in normotensive rats. In contrast to enflurane, hypertensive rats anesthetized with halothane demonstrated significant changes in flow to heart, skin, kidneys, muscle, stomach and small intestine when compared with normotensive rats anesthetized with halothane. Whether these decreases

in flow in hypertensive rats anesthetized with halothane or enflurane are harmful could not be ascertained from these studies. Investigation of tissue oxygen tensions and/or lactate measurements in these tissues would be useful to document the significance of these changes.

The clinical implications of these studies in renovascular hypertensive rats include the suggestion that halothane and enflurane decrease blood pressure by decreasing cardiac output while peripheral resistance actively increases. Similar results in humans receiving halothane anesthesia have been reported.<sup>4</sup> This increase in resistance is at the expense of flow to vital organs such as heart, kidney, and the splanchnic bed. The expected decrease in sympathetic nervous system activity, resulting from the anesthetics, appears operative in hypertensive rats. Without such a decrease in sympathetic tone, further decreases in blood flow to organs might have been seen. Finally, the renin-angiotensin system exerts considerable control of blood pressure in this form of hypertension both in the awake and anesthetized state. The degree of blood pressure support cannot be predicted from the measurement of plasma renin activity.

## References

1. Veterans Administration Co-operative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mmHg. *JAMA* 202:1028-1034, 1957
2. Veterans Administration Co-operative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressure averaging 90 through 114 mmHg. *JAMA* 213:1143-1151, 1970
3. Report of a cooperative randomized controlled trial: Control of moderately raised blood pressure. *Br Med J* 3:434-438, 1973
4. Prys-Roberts C, Mellocke R, Föex P: Studies of anaesthesia in

- relation to hypertension I: Cardiovascular responses of treated and untreated patients. *Br J Anaesth* 43:122-137, 1971
5. Prys-Roberts C: Interactions of anaesthesia and high pre-operative doses of B-receptor antagonists. *Acta Anaesthesiol Scand (Suppl)* 76:47-53, 1982
  6. Goldman L, Caldera D: Risks of general anesthesia and elective operation in the hypertensive patient. *ANESTHESIOLOGY* 50:285-292, 1979
  7. Goldblatt HJ, Lynch RF, Hanzal RF, Summerville WW: Studies on experimental hypertension I. The production of persistent elevation of systolic blood pressure by means of renal ischemia. *J Exp Med* 59:347-354, 1934
  8. Miller ED, Samuels AI, Haber E, Barger AC: Inhibition of angiotensin conversion in experimental renovascular hypertension. *Science* 177:1108-1109, 1972
  9. Streeton DH, Friedberg JM, Anderson GH, Dalakos TG: Identification of angiotensinogenic hypertension in man using 1-Sar<sup>8</sup>-Ala-angiotensin II (Saralasin P-1113). *Circ Res* 36-37 (suppl):1-125-1-132, 1975
  10. White PF, Johnston RR, Eger EI: Determination of anesthetic requirement in rats. *ANESTHESIOLOGY* 40:52-57, 1974
  11. DiFazio CA, Niederlehner JR, Burney RG: The anesthetic potency of lidocaine in the rat. *Anesth Analg* 55:818-821, 1976
  12. Ishikawa I, Hollenberg N: Blockade of the systemic and renal vascular actions of angiotensin II with 1-Sar<sup>8</sup>-ALA analogue in the rat. *Life Sci* 17:121-130, 1975
  13. Haber E, Koerner T, Page LB, Kliman B, Purnock AJ: Application of radioimmunoassay for angiotensin I to the physiologic measurements of plasma renin activity in normal human subjects. *J Clin Endocrinol Metab* 29:1349-1355, 1969
  14. Kissinger PT, Riggin RM, Alcorn RL, Rau LD: Estimation of catecholamines in urine by high performance liquid chromatography with electrochemical detection. *Biochem Med* 13:299-306, 1975
  15. Miller ED, Kistner JR, Epstein RM: Whole-body distribution of radioactively labelled microspheres in the rat during anesthesia with halothane, enflurane or ketamine. *ANESTHESIOLOGY* 52:296-302, 1980
  16. Miller ED, Longnecker DE, Peach MJ: The regulatory function of the renin-angiotensin system during general anesthesia. *ANESTHESIOLOGY* 48:399-403, 1978
  17. Miller ED, Ackerly JA, Peach MJ: Blood pressure support during general anesthesia in a renin-dependent state in the rat. *ANESTHESIOLOGY* 48:404-408, 1978
  18. Miller ED, Beckman JJ, Woodside JR, Althaus JS, Peach MJ: Blood pressure control during anesthesia: Importance of the peripheral sympathetic nervous system and renin. *ANESTHESIOLOGY* 58:32-37, 1983
  19. Tagawa H, Gutman FD, Haber E, Miller ED, Samuels AI, Barger AC: Reversible renovascular hypertension and renal arterial pressure. *Proc Soc Exp Biol Med* 146:975-982, 1974
  20. Miller ED, Samuels AI, Haber E, Barger AC: Inhibition of angiotensin conversion and prevention of renal hypertension. *Am J Physiol* 228:448-453, 1975
  21. Samuels A, Miller ED, Fray C, Barger AC: Renin-angiotensin antagonists and the regulation of blood pressure. *Fed Proc* 35:2512-2520, 1976
  22. Ackerly JA, Blumberg AL, Brooker G, Peach MJ: Angiotensin II on the release of DBH and atrial cyclic AMP concentrations. *Am J Physiol* 235:H281-H288, 1978
  23. Antonaccio MJ, Ferrone RA, Waugh M, Harris D, Rubin B: Sympathoadrenal and renin-angiotensin systems in the development of two-kidney, one clip renal hypertension in rats. *Hypertension* 2:723-731, 1980
  24. Flohr H, Breull W, Dahmers HW, Redel D, Conradi H, Stoepel K: Regional distribution of vascular resistance in two models of experimental renovascular hypertension. *Pflugers Arch* 362:157-164, 1976
  25. Knight PR, Lane GA, Nickolls MG, Tait AR, Nahrwold ML, Hensinger RN, Cohen PJ: Hormonal and hemodynamic changes induced by pentolinium and propranolol during surgical correction of scoliosis. *ANESTHESIOLOGY* 53:127-134, 1980
  26. Miller ED, Gianfagna W, Ackerly JA, Peach MJ: Converting-enzyme activity and pressor responses to angiotensin I and II in the rat awake and during anesthesia. *ANESTHESIOLOGY* 50:88-92, 1979
  27. Ganten D, Kusumotor M, Constantopoulos G, Ganten U, Boucher R, Genest J: Iso-renin, electrolytes and catecholamines in dog brain: Possible interrelationship. *Life Sci* 12:1-8, 1973
  28. Gould AB, Skeggs LT, Kahn JR: Presence of renin activity in blood vessel walls. *J Exp Med* 119:289-394, 1964
  29. Longnecker DE, McCoy S, Drucker WR: Anesthetic influence on response to hemorrhage in rats. *Circ Shock* 6:55-60, 1979
  30. Bavister PH, Longnecker DE: Influence of anaesthetic agents on the survival of rats following acute ischaemia of the bowel. *Br J Anaesth* 51:921-925, 1979
  31. Katholi RE, Whitlow PL, Winternitz SR, Oparil S: Importance of the renal nerves in established two-kidney, one clip Goldblatt hypertension. *Hypertension* 4 (Suppl 11):11-166-11-174, 1983
  32. Roizen MF, Moss J, Henry DP, Kopin IJ: Effects of halothane on plasma catecholamines. *ANESTHESIOLOGY* 41:432-439, 1974
  33. Depocas F, Behrens WA: Effects of handling, decapitation, anesthesia, and surgery on plasma noradrenaline levels in the white rat. *Can J Physiol Pharmacol* 55:212-219, 1977