

The Hemodynamic Response to Isoflurane is Altered in Genetically Hypertensive (SHR), as Compared With Normotensive (WKY), Rats

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The authors compared the hemodynamic effects of isoflurane anesthesia in normotensive (WKY) and genetically hypertensive (SHR) rats. Eighteen male SHR and 18 WKY rats were subdivided into conscious animals and those anesthetized with isoflurane, 1.2 vol% inspired. During brief isoflurane anesthesia, cannulae were placed in the left cardiac ventricle, the femoral artery, and the femoral vein. Central and regional hemodynamics were determined with ⁸⁵Sr-labeled microspheres (15 ± 1 μm) using the reference sample technique in both conscious and anesthetized animals. Isoflurane anesthesia caused similar reductions in mean arterial blood pressure (MAP) in all rats. This was due to a significant decrease in systemic vascular resistance in WKY rats, whereas MAP declined due to a significant decrease in cardiac output in SHR rats. In the anesthetized WKY rat, the decrease in total systemic vascular resistance resulted from significant decreases in vascular resistance of the brain and nonrespiratory skeletal muscles. In the anesthetized SHR rat, both decreases (cerebellum, hepatic artery) and increases (GI tract, skin, diaphragm) in regional vascular resistances occurred, resulting in no net change in total systemic vascular resistance. In both SHR and WKY rats, isoflurane redistributed blood flow in favor of the brain at the expense of blood flow to the GI tract, diaphragm, and skin. Blood flows to the liver, GI tract, and skin were significantly less in the anesthetized SHR as compared with WKY rats. It is concluded that isoflurane influences central and regional hemodynamics differently in hypertensive, as compared with normotensive, rats. (Key words: Anesthetics, volatile; Isoflurane. Blood pressure: drug effect; hypertension; measurement; peripheral vascular resistance. Measurement techniques: blood pressure; microspheres; organ blood flow.)

RESULTS FROM STUDIES in normotensive humans and animals suggest that, in clinical concentrations, isoflurane has relatively minor effects on cardiac output and blood flow to vital organs.¹⁻⁷ However, the hemodynamic effects of isoflurane in hypertensive patients and animals are not well documented, and there are several reasons to suspect that isoflurane may affect the circulation differently in hypertensive, as compared with normotensive, humans and animals. First, hypertensive rats demonstrate altered vascular reactivity to a variety of vasoactive stimuli, including both vasoconstrictors and vasodilators.^{8,9} Second,

halothane and enflurane altered hemodynamics differently in normotensive, as compared with chronically hypertensive, rats.¹⁰ Finally, clinical studies suggest that responses to anesthetics are altered in hypertensive humans.^{11,12} The present study was designed to determine whether the central and regional hemodynamic responses to isoflurane were similar in normotensive, *versus* genetically hypertensive, rats.

Materials and Methods

Studies were performed on 18 spontaneously hypertensive (SHR; 286 ± 6 g) and 18 normotensive (WKY; 290 ± 4 g) male rats (12-16 weeks of age for each; supplied by Charles River Laboratories). The animals were allocated into two groups: conscious animals, and those anesthetized with isoflurane. During brief isoflurane anesthesia (1.4-1.9 vol% inspired), polyethylene (PE-50) cannulae were placed in the left cardiac ventricle (*via* the right carotid artery) and the left femoral artery and vein. A tracheostomy was performed in those which were to remain anesthetized, then the wounds were closed and coated with lidocaine gel. All rats received 2 ml heparinized blood from donor rats to replace blood loss associated with the operation. The femoral arterial catheter was connected to a standard pressure transducer (Gould Statham Corporation, Hato Rey, Puerto Rico) and arterial pressure was recorded continuously. Animals in the conscious groups were allowed to recover for 2 h while restrained in a commercially available rat restraining cage. Animals in the anesthetized groups were paralyzed with pancuronium bromide (1 mg · kg⁻¹ iv), and isoflurane, 1.2 vol% inspired, was administered by controlled ventilation (F_IO₂ = 0.3) to maintain normocarbica. In all animals, rectal temperature was measured and maintained at 36-38° C by a heat lamp. Two hours of isoflurane anesthesia (an initial hour at an inspired concentration of 1.4-1.9 vol% and a second hour at 1.2 vol% inspired) has been shown to result in a small (3-6%) but relatively constant difference between inspired and alveolar anesthetic concentrations (F_I/F_A) for isoflurane, so that anesthetic depth should have remained constant throughout these experiments.¹³ After 1 h of stable anesthesia (or 2 h after recovery from anesthesia in the conscious animals), arterial P_O₂, P_{CO}₂, pH, and hematocrit were determined and cardiac output and regional blood flows to 15 tissues were measured using radiolabeled microspheres. Blood gas

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TABLE 1. Central Hemodynamics and Arterial Blood Values in SHR and WKY Rats. Absolute Values (Conscious) and Relative Changes (%) during Isoflurane Anesthesia

	Conscious (Absolute Values)		Response to Isoflurane (% Change from Conscious Value)	
	WKY	SHR	WKY	SHR
MAP (mmHg)	124 ± 4	168 ± 5*	-31 ± 5†	-22 ± 7†
CO (ml · min ⁻¹)	99 ± 4	103 ± 3	-6 ± 5	-22 ± 3*†
SVR (mmHg · ml ⁻¹ · min)	1.3 ± 0.1	1.6 ± 0.1*	-26 ± 6†	2 ± 12
P _{aO₂} (mmHg)	92 ± 4	82 ± 2	-9 ± 8	43 ± 8*†
P _{aCO₂} (mmHg)	37 ± 2	34 ± 1	-7 ± 3	-1 ± 3
H ⁺ (nEq · l ⁻¹)	39.5 ± 0.8	38.2 ± 1.3	-1 ± 2	-3 ± 2
(pH)	(7.40 ± 0.01)	(7.42 ± 0.03)		
Hct (%)	43 ± 2	46 ± 1	-7 ± 2	-1 ± 1
HR (bpm)	392 ± 8	457 ± 6*	-17 ± 4†	-23 ± 2†

Values are mean ± SEM.

*P < 0.02 vs. WKY; †P < 0.02 vs. conscious by Student's two sample *t* test.

measurements were performed using a standard blood gas analyzer (Radiometer BMS 3, PHM 73, Radiometer America, Cleveland, OH). Hematocrit was determined by the micromethod.

Approximately 80,000 ⁸⁵Sr labeled microspheres (15 ± 1 μm) in 0.2 ml suspending solution were thoroughly stirred and injected into the left cardiac ventricle. The catheter was flushed with saline, 0.4 ml. Arterial blood was removed by a constant withdrawal pump (withdrawal rate 0.5 ml · min⁻¹) for 10 s before, and 50 s after, the injection of microspheres. The rats were killed by an intravenous injection of KCl after the microspheres had been injected. The organs were removed, blotted on filter paper, weighed, and placed in counting tubes. Radioactivity was determined in the following tissues: brain (subdivided into cerebrum and cerebellum), heart, lungs, kidneys, GI tract (stomach, small bowel, large bowel, and cecum), spleen, liver, diaphragm, rectus abdominis muscle, gastrocnemius muscle, tibialis anterior muscle, psoas muscle, cremaster muscle, and skin (aliquots of skin and liver were sampled due to the size of the organs). Radioactivity of the reference samples and organs was measured in a well-type gamma counter (Compugamma 1282-002, LKB Instruments Incorporated, Gaithersburg, MD). Cardiac output (ml · min⁻¹) was determined by the equation: CO = total injected radioactivity × reference sample flow ÷ reference sample radioactivity. Injected radioactivity was determined by counting radioactivity in the syringe before and after injection of the microspheres. Regional blood flows (ml · min⁻¹ · 100g⁻¹) were determined by substituting organ activity for total injected activity in the above equation. Similar flow rates in the left and right kidneys were used as a criterion for adequate mixing of the microspheres; differences of more than 20% indicated insufficient mixing, and data of such animals were not included in the analysis. Portal venous flow was estimated as proposed by Ross and Daggy¹⁴ and reported in previous studies.^{7,15} Organ vascular resistances were calculated as

the quotient of mean arterial pressure and organ blood flow (mmHg · ml⁻¹ · min · g). Central venous pressure was assumed to be zero and portal venous pressure to be 10 mmHg for these calculations.¹⁶ Data during anesthesia were normalized and presented as percent change from control (*i.e.*, the values in conscious rats).

To further investigate the effects of isoflurane on resistance vessels in SHR and WKY rats, additional experiments were performed using the cremaster muscle preparation. Six WKY and five SHR rats were anesthetized with chloralose, 60 mg · kg⁻¹, plus urethane, 800 mg · kg⁻¹, IP. The animals' tracheas were intubated and they breathed room air spontaneously throughout the experiment. The left cremaster muscle was exposed through a scrotal incision and prepared for observation of the microcirculation according to the technique of Baez.¹⁷ The cremaster muscle was suffused continuously with a warmed, buffered, balanced salt solution (containing in mM: NaHCO₃, 25.5; NaCl, 131.9; KCl, 4.7; CaCl₂, 2.0; MgSO₄, 1.17), which was equilibrated with 95% nitrogen and 5% CO₂ without (control period) or with (treatment period) isoflurane, 1.25 or 2.5 vol%. The protocol consisted of three 10-min intervals: a control period (suffusion solution only), a treatment period (isoflurane equilibrated suffusion solution), and a recovery period (suffusion solution only). Internal diameters of fourth order arterioles were measured at 30-s intervals throughout. Arteriolar diameters were normalized as percent of control and average responses for the 10-min treatment period were calculated. All values are presented as mean ± standard error of the mean (SEM). Statistical comparisons were made using Student's two-sample *t* test, using Bonferroni's correction for multiple comparisons; *P* < 0.02 was considered to be significant.

Results

Results for central hemodynamics and arterial blood values are illustrated in table 1. Cardiac outputs were sim-

TABLE 2. Organ Blood Flow $\text{ml} \cdot \text{min}^{-1} \cdot 100\text{g}^{-1}$ in Conscious WKY and SHR Rats and Isoflurane-Induced Relative Changes (% Change From Control)

	Conscious		Response to Isoflurane (% Change)	
	WKY	SHR	WKY	SHR
Cerebrum	96 ± 6	103 ± 6	18 ± 5	9 ± 8
Cerebellum	86 ± 9	107 ± 5	74 ± 18†	27 ± 10†
Heart	491 ± 49	529 ± 39	-27 ± 6	-41 ± 7†
Kidneys	866 ± 50	638 ± 57*	-37 ± 6†	-11 ± 7*
Spleen	172 ± 18	130 ± 18	-26 ± 9	-13 ± 19
GI tract	264 ± 25	259 ± 18	-32 ± 6†	-48 ± 4†
Hep. artery	21 ± 4	13 ± 3	-12 ± 6	35 ± 17*
Tot. hepatic	66 ± 12	145 ± 17	-21 ± 6	-41 ± 4*†
Skin	17 ± 1	14 ± 1	-43 ± 11†	-62 ± 4†
Diaphragm	51 ± 7	73 ± 7	-56 ± 6†	-77 ± 3*†
Rect. abd. m.	10 ± 2	11 ± 2	31 ± 27	4 ± 17
Gastrocn. m.	7 ± 1	13 ± 2*	549 ± 118†	235 ± 92
Tib. ant. m.	8 ± 1	18 ± 5	484 ± 114†	121 ± 50*
Psoas m.	11 ± 3	22 ± 5	92 ± 22†	-1 ± 22*
Cremaster m.	5 ± 1	6 ± 2	4 ± 26	-30 ± 13

Values are Means ± SEM.

* $P < 0.02$ vs. WKY; † $P < 0.02$ vs. conscious by Student's two sample t test.

ilar in conscious SHR and WKY rats; arterial hypertension in the SHR rats was due to the significantly greater systemic vascular resistance. Isoflurane anesthesia decreased mean arterial pressure (MAP) significantly ($P < 0.02$) in all animals, and the relative magnitude of this decrease was similar in WKY ($-31 \pm 5\%$) and SHR ($-22 \pm 7\%$) rats. Whereas systemic vascular resistance decreased significantly ($-26 \pm 6\%$, $P < 0.01$) in WKY rats receiving iso-

flurane, no change in systemic vascular resistance occurred in the anesthetized SHR rats. Conversely, isoflurane caused a significant ($P < 0.001$) decrease in cardiac output ($-22 \pm 3\%$) in SHR rats, but cardiac output was unchanged in WKY rats receiving isoflurane. Values for PaCO_2 , hydrogen ion concentration, and hematocrit were similar in all rats. PaO_2 values were similar in conscious SHR and WKY rats, but PaO_2 increased significantly ($43 \pm 8\%$) in the SHR rats receiving isoflurane. Heart rate decreased similarly during isoflurane anesthesia in WKY and SHR rats.

Table 2 shows the absolute values for regional blood flows in conscious SHR and WKY rats and the relative change in these values resulting from isoflurane treatment. In general, organ blood flows were similar in conscious normotensive and hypertensive animals. Among 15 tissues, differences were observed only in blood flows to the kidneys and gastrocnemius muscle. Isoflurane anesthesia did not alter cerebral blood flow values in SHR and WKY rats. However, in all anesthetized animals, cerebellar blood flow was significantly increased; this increase was similar in the WKY as compared to the SHR, although values in WKY rats tended to be greater ($74 \pm 18\%$ vs. $27 \pm 10\%$, respectively). A decrease in myocardial blood flow was observed in hypertensive animals receiving isoflurane, whereas renal blood flow was significantly reduced only in the WKY. Blood flow to the GI tract decreased to a similar degree in anesthetized SHR and WKY rats. Total hepatic blood flow did not change in the WKY, but decreased significantly ($P < 0.02$) in the anesthetized SHR. Hepatic arterial blood flow did not change during isoflurane anesthesia. Cutaneous blood flow was significantly less in all anesthetized animals than in conscious rats, although the decrease tended to be greater in SHR ($-62 \pm 4\%$), than in WKY ($-43 \pm 11\%$), rats. Diaphragmatic blood flow decreased in all animals receiving isoflurane, but the decrease was greater in SHR ($-77 \pm 3\%$), as compared with WKY ($-56 \pm 6\%$), rats. In the anesthetized WKY, blood flow to the gastrocnemius, tibialis, and psoas muscles increased, whereas, in the isoflurane-treated SHR rat, blood flow to the nonrespiratory skeletal muscles did not change. Figure 1 illustrates the absolute values for regional blood flows in SHR and WKY rats during isoflurane anesthesia. Absolute blood flows to the GI tract, liver, and skin were significantly less in SHR, than in WKY, rats. No differences in blood flow values were observed among the other organs.

The isoflurane-induced changes in regional vascular resistances are illustrated in figure 2. In WKY rats (fig. 2A), significant changes in regional vascular resistances were observed only in the brain (cerebellum and total brain) and the skeletal muscles, and the prevalent response in these tissues was a decrease in resistance. In the SHR rats (fig. 2B), significant increases in regional vascular re-

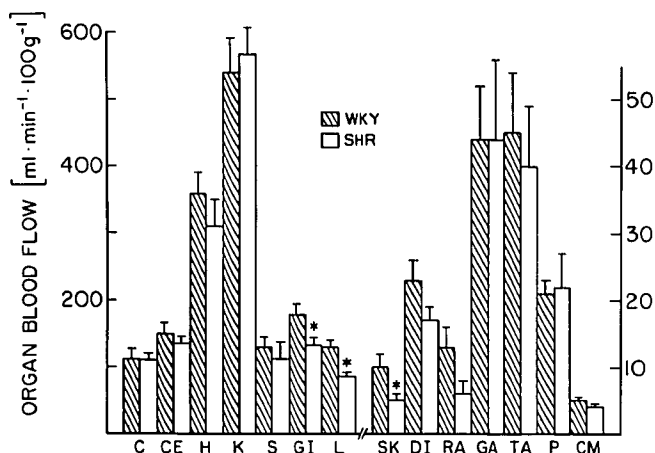


FIG. 1. Absolute organ blood flows ($\text{ml} \cdot \text{min}^{-1} \cdot 100\text{g}^{-1}$) during isoflurane anesthesia in SHR and WKY rats. Open bars = SHR; hatched bars = WKY; C = cerebrum; Ce = cerebellum; H = heart; K = kidneys; S = spleen; GI = GI tract; L = liver; Sk = skin; DI = diaphragm; RA = rectus abdominis muscle; GA = gastrocnemius muscle; TA = tibialis anterior muscle; P = psoas muscle; CM = cremaster muscle. Values are mean ± SEM. *Significantly different from WKY ($P < 0.02$ by Student's two sample t test).

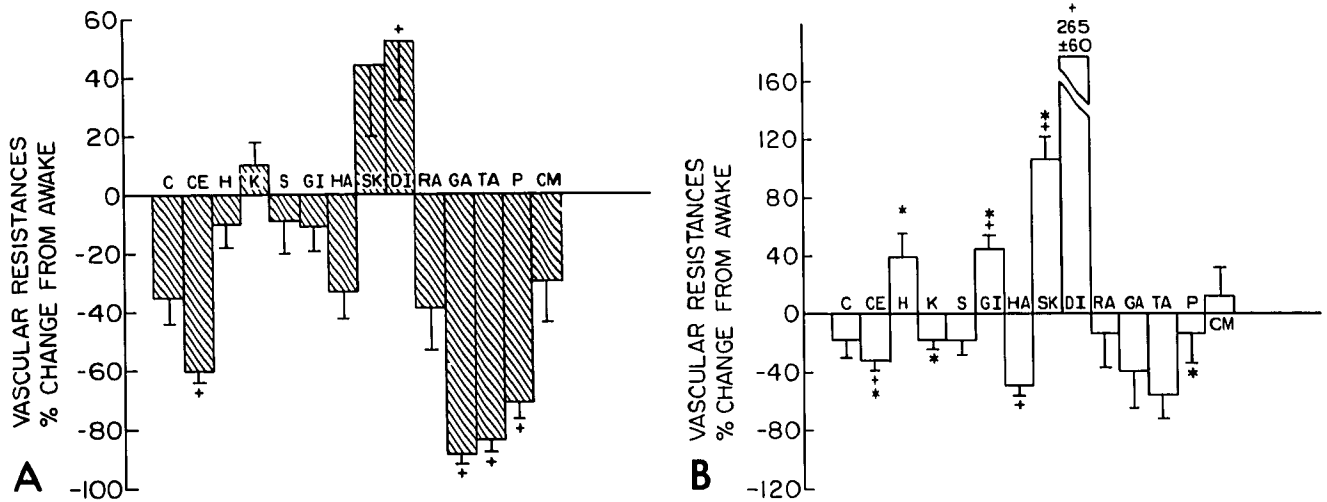


FIG. 2. Isoflurane anesthesia induced relative changes (%) in regional vascular resistances in WKY (A) and SHR (B) rats. C = cerebrum; Ce = cerebellum; H = heart; K = kidneys; S = spleen; GI = GI tract; L = liver; Sk = skin; DI = diaphragm; RA = rectus abdominis muscle; GA = gastrocnemius muscle; TA = tibialis anterior muscle; P = psoas muscle; CM = cremaster muscle. Values are mean \pm SEM. *Significantly different from conscious; **significantly different from response in WKY ($P < 0.02$ by Student's two sample *t* test).

stances occurred in the GI tract, skin, and diaphragm. Significant decreases in vascular resistances were observed in the cerebellum and hepatic artery; there was a slight tendency for vasodilation in the nonrespiratory skeletal muscles, but this trend did not reach statistical significance.

Figure 3 illustrates the effects of topically administered isoflurane on rat cremaster muscle arterioles. In WKY and SHR rats, topical isoflurane (1.25% or 2.5% in the suffusion solution) resulted in a slight but significant arteriolar dilation.

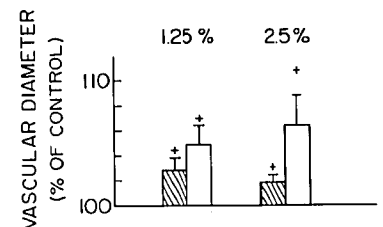
Discussion

In this study, we investigated the effects of isoflurane on hemodynamics in normotensive and chronically hypertensive adult rats. In the conscious SHR rat, increased systemic vascular resistance was responsible for the increased mean arterial pressure. The results have been reported for the conscious adult SHR rat by others,^{18,19} and similar hemodynamics were also observed in humans with essential hypertension.²⁰ The possible causes of the increased vascular resistance in chronically hypertensive rats are many, and include both a decrease in arteriolar diameter due to an increased sympathetic activity or hyperresponsiveness to vasoactive agents,^{21,22} and a reduction in capillary density (rarefaction).²³ The SHR rat is reportedly a suitable hemodynamic model of essential hypertension in humans,²⁴ and the increased systemic vascular resistance in our rats is similar to that seen in humans with essential hypertension. In normotensive human vol-

unteers, isoflurane anesthesia decreased mean arterial pressure primarily by decreasing systemic vascular resistance.^{2,25} We observed similar hemodynamic effects of isoflurane in our WKY rats, and we reported a similar hemodynamic response to isoflurane in Sprague-Dawley rats.⁷ Thus, there are similarities between humans and rats, both in the hemodynamic changes associated with hypertension, and in the hemodynamic responses to isoflurane.

The striking finding in our study was that isoflurane affected central and regional hemodynamics differently in SHR and WKY rats. In WKY rats, the decrease in mean arterial pressure was associated with a decrease in systemic vascular resistance, whereas cardiac output remained unchanged; results consistent with previous findings in normotensive humans and rats.^{2,7} A direct relaxing effect of isoflurane on vascular smooth muscle²⁶ or a decrease in sympathetic efferent nerve activity^{27,28} may be

FIG. 3. Relative change in diameter of cremaster muscle arterioles after topical administration of isoflurane. Control diameters were $10.7 \pm 0.5 \mu\text{m}$ in SHR and $10.8 \pm 0.4 \mu\text{m}$ in WKY rats. Open bars = SHR; hatched bars = WKY. Values are mean \pm SEM. *Significantly different from control; **significantly different from response in WKY ($P < 0.05$ by Student's two sample *t* test).



important mechanisms responsible for this vasodilation. In WKY rats, isoflurane anesthesia caused decreases in vascular resistances in the cerebellum and the majority of nonrespiratory skeletal muscles, but no significant changes were observed in the vascular beds of the kidneys, GI tract, heart, or hepatic artery. These results are in agreement with previous reports demonstrating that isoflurane mildly dilates the cerebral vasculature of animals,^{7,29,30} and that isoflurane decreases skeletal muscle vascular resistance in humans. However, vasodilation was not observed in the skeletal muscles of swine receiving isoflurane,³⁰ nor was systemic vascular resistance decreased in this species either. In a previous study using spontaneously breathing Sprague-Dawley rats, little decrease in vascular resistance was observed in skeletal muscles.⁷

Isoflurane decreased MAP in chronically hypertensive rats, but this resulted from a significant decrease in cardiac output, whereas systemic vascular resistance remained unchanged. We do not have direct evidence to explain why isoflurane decreased cardiac output in SHR, but not WKY, rats. Possibly, the reduced afterload in WKY rats counteracted factors (*e.g.*, negative inotropism or decreased preload) which otherwise would have decreased cardiac output.³¹ In contrast, the increased systemic vascular resistance, which persisted during isoflurane in SHR rats, may have potentiated any tendency for decreased ventricular ejection.

Although it is a common clinical impression that arterial pressure declines more markedly during anesthesia in hypertensive than in normotensive patients, this difference was not observed in the present study. The relative decrease in MAP was similar in SHR ($-22 \pm 7\%$) and WKY ($-31 \pm 5\%$) rats receiving isoflurane (although, of course, the absolute decrease was greater in the hypertensive rats due to greater initial values). Further data reported by Miller *et al.*¹⁰ for both halothane and enflurane demonstrated that the anesthetic-induced decreases in MAP were relatively greater in the normotensive (-40%), as compared to hypertensive (-25%), rats.

The unchanged total systemic vascular resistance in SHR rats did not result from an absence of changes in individual regional vascular resistances. During isoflurane anesthesia in SHR rats, significant decreases in vascular resistances were observed in the cerebellum and the hepatic artery, but these decreases were opposed by increased vascular resistances in the skin, GI tract, and diaphragm; responses which, except for the diaphragm, were not observed in the isoflurane-treated WKY rats.

Our data do not identify the mechanisms responsible for the differing effects of isoflurane on regional vascular resistances in SHR and WKY rats. Because no consistent decrease in skeletal muscle vascular resistance was ob-

served in the SHR rats during isoflurane, one might postulate that the direct vasodilating effects of isoflurane were less in SHR, as compared with WKY, rats. In an attempt to test this hypothesis, isoflurane was administered topically to the cremaster muscle of SHR and WKY rats. Small but significant arteriolar dilation occurred in both groups. These responses were similar in SHR, as compared to WKY, rats. At least in the cremaster skeletal muscle vasculature, these results do not support the hypothesis that the direct vasodilating effect of isoflurane is less in SHR, than in WKY, rats.

In the SHR rat receiving isoflurane, increases in vascular resistances of skin and GI tract may represent a reflex response to the decrease in mean arterial pressure, and they may reflect the increased sympathetic activity which occurs in these animals.²² For example, these tissues are among the principal sites for vasoconstriction in response to acute hemorrhage, which is a powerful stimulus for increased sympathetic activity.³² Alternatively, other factors, such as the renin-angiotensin system,³³ may be involved also. In the SHR rat, vasoconstriction in the splanchnic viscera appears to be of special interest in view of the reports by Krogh³⁴ and Coleman *et al.*,³⁵ who reported that an increase in arterial vascular resistance of the splanchnic circulation can bring about an increase in cardiac output by diverting blood away from the splanchnic portal system. This mechanism might have been operative in our anesthetized SHR rats in order to prevent further decreases in cardiac output and mean arterial pressure during isoflurane.

Isoflurane did not alter cerebral blood flow, but cerebellar blood flow was increased in both animal strains. In a previous study,⁷ we reported increases in both cerebral and cerebellar blood flows during isoflurane anesthesia in Sprague-Dawley rats, but those animals breathed spontaneously, whereas controlled ventilation and constant P_{aCO_2} was employed in the present study. A greater cerebellar than cerebral blood flow during isoflurane anesthesia in rats was also observed in our previous study,⁷ and a similar observation has been reported recently in dogs.³⁶

A decrease in myocardial blood flow was observed in SHR rats receiving isoflurane. Presumably, this reflects the decrease in myocardial oxygen demand in the anesthetized animals, as evidenced by reductions in both heart rate and blood pressure. However, the reported effects of isoflurane on myocardial blood flow in other species are variable. Although isoflurane also caused a dose-dependent decrease in myocardial blood flow in one study in dogs,³¹ others have reported increased⁶ or unchanged³⁷ blood flows in this species, and isoflurane did not alter myocardial blood flow in humans with coronary artery disease.³⁸ However, differences in anesthetic depth, flow

measurement techniques, species, and experimental design make precise comparisons difficult.

Renal blood flow decreased in the WKY rats receiving isoflurane, a phenomenon observed during general anesthesia in humans also.⁵⁹ In dogs, however, no changes in renal blood flow were observed.⁶ We are uncertain why renal blood flow did not change in the anesthetized SHR rat, but the low initial renal blood flow in the conscious state might have limited any further decrease in these animals.

Absolute blood flows to the liver, gastrointestinal organs, and skin were less during isoflurane anesthesia in SHR rats, as compared with WKY rats (fig. 1). Apparently cardiac output was reduced at the expense of flow to these tissues in SHR rats. It is of interest that hepatic arterial blood flow tended to increase in the SHR rat receiving isoflurane, suggesting that oxygen delivery to the liver was not as compromised as the decrease in total hepatic blood flow would suggest, and implying that control of overall hepatic blood flow (the so-called "reciprocity of hepatic blood flow") was intact in these animals.

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