TITLE: EFFECT OF HALOTHANE, ENFLURANE OR ISOFLURANE ON THE REGULATION OF TOTAL HEPATIC BLOOD FLOW IN RATS

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Introduction. Two vascular systems supply blood flow to the liver: the portal venous and hepatic arterial systems. A reciprocal relationship, termed "reciprocity of blood flow," has been demonstrated for these systems in several species, including humans, dogs and rats. The relationship is such that changes in portal venous flow (PVF) are accompanied by qualitatively similar changes in hepatic arterial vascular resistance (HAR), presumably in an attempt to minimize changes in total hepatic blood flow. Thus decreases in PVF are usually accompanied by decreases in HAR so that overall changes in hepatic blood flow are minimized. In the present study, we investigated the influences of three volatile anesthetics on this hepatic vascular autoregulatory phenomenon. Hypovolemia was used to alter PVF and both PVF and HAR were determined before and after hemorrhage.

Methods. Thirty-seven male Sprague-Dawley rats (348±4 g) were divided into four groups according to anesthetic exposure: awake animals and those receiving halothane, enflurane or isoflurane. Cannulae were placed in the left femoral artery and vein and the left cardiac ventricle. Inspired concentrations were controlled to maintain the minimum alveolar concentration for each anesthetic. All animals breathed spontaneously throughout the experiment (FIO_2=0.3). After a two-hour stabilization period, 30% of estimated blood volume was withdrawn gradually over 10 min. Immediately before and 20 min after hemorrhage, PVF and hepatic arterial blood flows [$ml \cdot min^{-1} \cdot 100g^{-1}$] were measured by the microsphere method (^{85}Sr, ^{141}Ce-labelled 15 μm microspheres, respectively). Arterial blood gas samples were analyzed for PO_2, PCO_2 and pH at these times also. HAR was calculated as the quotient of mean arterial pressure and hepatic arterial blood flow. The quotient, ΔHAR/ΔPVF, was derived to describe the hepatic autoregulatory response to hemorrhage. The numerator of this quotient represents the absolute changes in HAR before and after hemorrhage, while the denominator represents the changes in PVF before and after hemorrhage. Statistical analyses were performed using Student's t-test for paired data within each group. Duncan's Multiple Range Test was used for multiple comparisons among groups. Significance was accepted if $p<0.05$. All data are presented as mean ± SEM.

Results. Results are summarized in the table. The quotient, ΔHAR/ΔPVF, was similar for awake animals and those receiving enflurane or isoflurane anesthesia, but this value was significantly decreased in animals anesthetized with halothane. Arterial blood gas values varied among the treatment groups, presumably due to the individual pharmacological properties of each anesthetic. Before hemorrhage, $PaCO_2$ was increased in animals receiving halothane or enflurane. After hemorrhage, $PaCO_2$ was greater in all those anesthetized as compared with the awake animals.

Discussion. The "reciprocity of flow" autoregulatory mechanism should be evidenced by a decrease in HAR in response to a decrease in PVF. In this study, hemorrhage caused a decrease in PVF in all animals. In awake animals and those receiving enflurane or isoflurane, HAR decreased in response to the reduced PVF, indicating that the "reciprocity of flow" mechanism was intact in these animals. Halothane impaired this hepatic autoregulatory mechanism, as evidenced by the marked alteration in the ΔHAR/ΔPVF value. Indeed, the changes in animals receiving halothane were such that decreased PVF was accompanied by increased HAR (as evidenced by a negative value for the ΔHAR/ΔPVF ratio). In rats anesthetized with halothane, reductions in PVF were accompanied by increases in HAR, a mechanism which would enhance the overall reduction in liver blood flow rather than minimize it. Although we cannot exclude possible $PaCO_2$ effects on HAR in this study, it is likely that these influences are of relatively minor importance. The changes in $PaCO_2$ after hemorrhage were relatively small in animals receiving enflurane (-11%) or isoflurane (-6%) suggesting that the magnitude of the $PaCO_2$ effect would be relatively minor in these animals. We conclude that halothane results in a major impairment of the normal hepatic vascular autoregulatory response (the "reciprocity of flow") in rats. Impairment of this response could contribute to the development of hepatic ischemia and potential cellular hypoxia in the livers of animals receiving halothane.

Table

Variable		A	H	E	I	Significant Differences (DMRT)
PaO_2 [mmHg]	N	118±3	86±6	82±7	99±5	A>E
	HE	119±4	110±8*	87±8	100±6	A>E
$PaCO_2$ [mmHg]	N	28±1	44±1	44±2	32±1	A,I<H,E
	HE	24±1	44±1	39±1*	30±2*	A<I<E<H
H^+ [nEq/L]	N	37.7±1.0	48.5±1.6	44.5±1.7	40.1±1.1	A<E,H;I<H
	HE	37.9±1.1	49.7±1.6	43.8±1.1	40.5±1.2	H>E>A;H>I
$\frac{\Delta HAR}{\Delta PVF} \times 10^2$ [$mmHg \cdot ml^{-2} \cdot min^2 \cdot g^2$]		3.23±1.17	-2.68±1.34	3.32±0.63	2.85±1.40	H<A,E,I

A = awake, H = halothane, E = enflurane, I = isoflurane; N = normovolemia, HE = 20 min after hemorrhage. *$p<0.05$ vs normovolemic values; DMRT = Duncan's Multiple Range Test.