Cardiac and Hepatic Metabolism in Spontaneously Hypertensive Rats Following Acute Blood Loss

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Seven spontaneously hypertensive rats (SHRs) and eight Wistar-ST rats were used to assess the influence of hemorrhage on myocardial and hepatic energy metabolism. They received 2% halothane and pancuronium, 0.3 $mg \cdot kg^{-1}$, during preparation. After discontinuation of halothane, blood (2 $ml \cdot 100g$ body $weight^{-1}$) was gradually withdrawn over a 5 min period from a femoral artery. Thirty min after induction of hemorrhage, the heart and liver were removed and myocardial and hepatic metabolites (ATP, lactate, pyruvate and glycogen) were measured by the enzymatic methods. Acidosis and decreased hematocrit were noted in the both groups after hemorrhage. Mean arterial pressure (MAP) in SHR was significantly higher than that in Wistar rat before hemorrhage. However, there were no significant differences in MAP and heart rate between the two groups after hemorrhage. Although there were no significant differences in cardiac metabolites, a significant decrease of hepatic ATP and an increase of hepatic lactate/pyruvate ratio were found in SHR when compared with Wistar rat. These results suggest that human hypertensive disease may run a high risk in connection with acute hemorrhage. (Key words: cardiac and hepatic metabolism, hemorrhagic shock, spontaneously hypertensive rat)

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The hypertensive individual may run a higher risk than the normotensive one in acute emergency situations such as hemorrhage. As a spontaneously hypertensive rat (SHR) is in many ways similar to essential hypertension in man[1], it is presently being used as a model for human essential hypertension[2–4]. A SHR has also been reported to be less able to tolerate than normotensive rats[5–9].

In the present study, SHRs and normotensive Wistar-ST rats were subjected to hemorrhage and the effects on arterial blood pressure, myocardial and hepatic metabolism have been compared.

Materials and Methods

Seven spontaneously hypertensive rats (SHRs) and 8 Wistar-ST rats

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were used to assess the influence of hemorrhage on myocardial and hepatic energy metabolism. They received 2% halothane and pancuronium, 0.3 $mg \cdot kg^{-1}$, during preparation. Following a tracheostomy, intermittent positive pressure ventilation was adjusted to maintain arterial P_{CO_2} (Pa_{CO_2}) at 40 ± 5 mmHg with 67% nitrogen and 33% oxygen. Electrocardiograms were recorded with a bioelectric amplifier (AB-621G, Nihonkohden, Japan). A Millar's microtip catheter pressure transducer (SPR-249, USA) was inserted into the right femoral artery to measure arterial pressure. A 24 gauge catheter was inserted into the left femoral artery for blood sampling. Rectal temperature was maintained at 37°C by external heating.

After surgical preparation, halothane was discontinued and thereafter hemorrhage (2 $ml \cdot 100g$ body $weight^{-1}$) was produced by gradual withdrawal of blood over 5 min from the femoral catheter using a syringe pump (Terumo, Co. Ltd.). Mean arterial pressure (MAP), heart rate (HR) and CO were measured every 5 min during the experiment. Arterial P_{O_2} (Pa_{O_2}), Pa_{CO_2}, pH and hematocrit (Ht) were measured from blood samples before and 30 min after induction of hemorrhage. Blood gas measurements were performed by a standard blood gas analyzer. Ht was determined by the micromethod.

Thirty min following induction of hemorrhage, the abdomen was opened and the entire heart and a part of the liver were removed and rapidly frozen between pre-cooled Wollenberger tongs, and submerged in liquid nitrogen. Their tissues were subsequently freeze-dried for 6 days. A part of each sample was extracted with perchloric acid and centrifuged at 3,000 xg. ATP, lactate and pyruvate levels were determined by spectrophotometrically by standard techniques according to Bergmeyer[10]. Another portion was placed in 30% KOH and digested in a boiling water bath. Tissue glycogen was extracted, hydrolyzed and assayed as the glucose equivalent[11]. All values were expressed as micromoles per gram of dry weight.

Significant differences were calculated using Student's tests for paired data to compare values before and after hemorrhage within each group. Student's non-paired tests were also used for unpaired data. A probability of $P < 0.05$ was regarded as statistically significant. The data were given as mean ± SD.

Results

MAP in SHRs was significantly higher than that in Wistar rats before hemorrhage. However, there were no significant differences in MAP and HR between the two groups after hemorrhage (fig. 1, 2).

Acidosis and decreased Ht were noted in the two groups after hemorrhage (table 1). Although no significant differences were detected in myocardial metabolites between the two groups, hepatic ATP content in the SHR group was significantly lower than that in the Wistar group. Hepatic lactate/pyruvate (L/P) ratio in the SHR group was significantly higher than that in the Wistar group (table 2).

Discussion

Our results indicate that metabolic responses to hemorrhage in SHRs were different from those in the normotensive rats and they are consistent with those of other studies, which indicate that the ability of SHRs to withstand hypotensive stress is less than that of normotensive controls[5–9]. This genetic dysfunction seems to be related to the difference of adrenoreceptors, hypertrophy of vascular smooth muscles[8] which decreases the reserve capacity

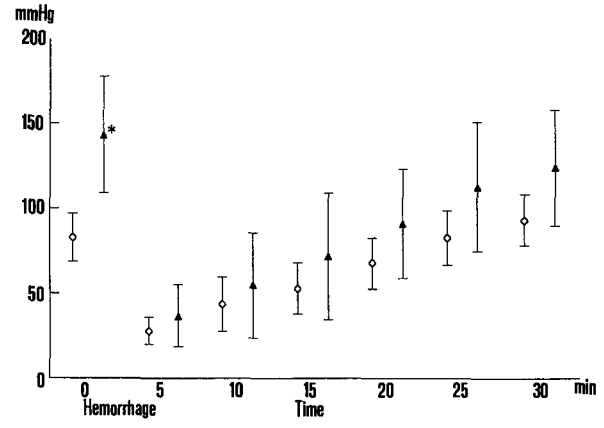

Fig. 1. Mean arteriall pressure changes in two groups.
*$P < 0.01$ as compared with a value for Wistar.
○ for Wistar rats and ▲ for SHRs.
Bars indicate ± SD.

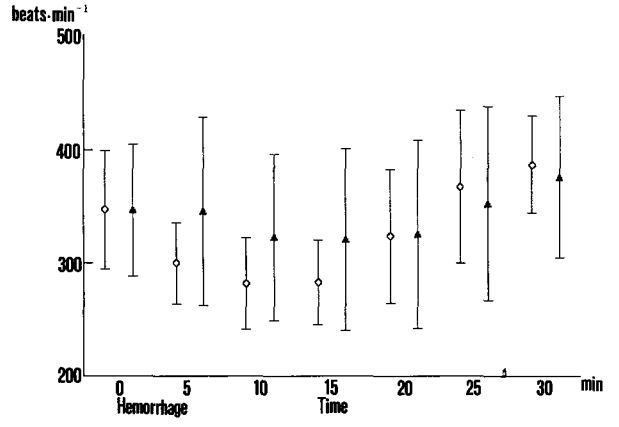

Fig. 2. Heart rate changes in two groups.
*$P < 0.01$ as compared with a value for Wistar.
○ for Wistar rats and ▲ for SHRs.
Bars indicate ± SD.

Table 1. Blood gas analysis and hematocrit

		Wistar (n=8)	SHR (n=7)
pH	pre	7.31 ± 0.04	7.37 ± 0.03
	post	7.23 ± 0.02*	7.28 ± 0.02*
P_{O_2}	pre	176 ± 21	180 ± 18
(mmHg)	post	166 ± 24	178 ± 20
P_{CO_2}	pre	41 ± 5	36 ± 3
(mmHg)	post	45 ± 5	42 ± 6
Base excess	pre	−4.8 ± 1.0	−3.4 ± 1.3
($mEq \cdot l^{-1}$)	post	−7.5 ± 2.4	−6.0 ± 2.5
Hematocrit	pre	47 ± 2	49 ± 1
	post	33 ± 6*	38 ± 3*

*$P < 0.01$, as compared with pre-values.

for compensatory venoconstriction[7], and reductions in tissue perfusion after hemorrhage[6,8]. Moreover, in the basal state SHRs already have a hyperactive sympathetic nervous system[12,13] and an increased sensitivity of vascular smooth muscles[14,15]. Such differences may more critically affect the compensatory capacity of SHRs than of normotensive rats following acute blood loss.

In the present study, the acute hemorrhage was preceded by halothane anesthesia during the preparation. Therefore, any remaining pharmacological effects of halothane would still affect the response of rats, since the influence of anesthesia may differ between normotensive and hypertensive rats[2–4].

Although there were no significant differences in myocardial metabolites between the two groups, values for hepatic ATP in the SHR group were

Table 2. Myocardial and hepatic metabolites in two groups

		Wistar (n=8)	SHR (n=7)
Heart	ATP^+	14.61 ± 1.31	13.85 ± 1.08
	$Glycogen^+$	108.2 ± 27.5	126.4 ± 19.2
	L/P	85.4 ± 13.1	74.3 ± 14.8
Liver	ATP^+	4.57 ± 0.86	3.35 ± 0.54*
	$Glycogen^+$	295.1 ± 113.2	256.2 ± 165.6
	L/P	77.1 ± 13.9	98.5 ± 12.9*

$^+$ $\mu mole \cdot g^{-1}$ dry tissue.
*$P < 0.01$ as compared with values for Wistar.

lower than that in the Wistar group. Hepatic L/P ratio in the SHRs was also significantly higher than that in the normotensive rats. These are consistent with other studies reported that effects of the blood loss on tissue metabolism were surprisingly severe in SHRs as compared to Wistar-Kyoto rats[5,16]. The reason for the metabolic deterioration of SHRs following blood loss seems to be an inadequate compensatory capacity. There were no significant differences in MAP between the two groups after hemorrhage. There are significant differences in vascular perfusion pressures needed for the maintenance of normal tissue homeostasis between SHRs and normotensive rats[16]. Therefore, the average of MAP in SHRs during the posthemorrhagic period may be too low to provide sufficient amounts of oxygen to important organs, including the liver.

It is well established that the raised circulating cathecolamines during hemorrhage increases glycogenolysis and hyperglycemia[17]. Strawitz et al.[18] found a correlation between survival times and the ability to maintain hyperglycemia in rats subjected to shock. Thus, hyperglycemia seems to be important for the tolerance to blood loss. Wennberg et al.[6] have reported the inability of SHRs to maintain hyperglycemia and short posthemorrhagic survival times in SHRs. Although blood glucose levels were not measured in the present study, there was no significant difference in the hepatic glycogen content between SHRs and normotensive rats.

It may be inappropriate to translate results obtained in animals directly to man with hypertension. However, our data suggest that human hypertensive disease may run a high risk in connection with acute hemorrhage.

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