Effects of α-Adrenergic Activation on the Shift of Electrolytes and Fluid after Hemorrhage in Rats

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Abstract To assess the effects of α-adrenergic activation on hemorrhage-induced shifts of $K^+$, $Na^+$ and fluid between the intravascular and extravascular spaces, we continuously measured changes in plasma concentrations of $K^+$ and $Na^+$ ($Δ[K^+]p$, $Δ[Na^+]p$) and blood volume ($ΔBV$) over 60 min after hemorrhage in nephrectomized rats. Hemorrhage was conducted over 5 min at the level of 0.5, 1.0 and 1.5% of body weight ($H_{0.5}$, $H_{1.0}$, $H_{1.5}$), and the result was compared with hemorrhage of 1.0% body weight after administration of α$_1$-adrenoreceptor antagonist prazosin (0.2 mg/kg, $H_{0.5}$). $Δ[K^+]p$ increased significantly ($p < 0.05$) after hemorrhage, and the peak value was proportional to the level of hemorrhage ($0.18 ± 0.08$, $0.62 ± 0.22$ and $1.64 ± 0.19$ meq/l in $H_{0.5}$, $H_{1.0}$ and $H_{1.5}$, respectively). $Δ[Na^+]p$ decreased significantly ($p < 0.05$) after hemorrhage, and the decrease was sustained until the end of the experiment ($−0.8 ± 0.6$, $−1.0 ± 0.5$ and $−2.2 ± 0.5$ meq/l in $H_{0.5}$, $H_{1.0}$ and $H_{1.5}$, respectively). In $H_{1.0}$, the increase in $Δ[K^+]p$ ($0.25 ± 0.09$ meq/l at the peak) and the decrease in $Δ[Na^+]p$ ($−0.2 ± 0.1$ meq/l at the bottom) were suppressed significantly ($p < 0.05$) compared to $H_{1.0}$. Although $ΔBV$ was greater in $H_{1.0}$ than $H_{1.0}$, plasma $K^+$ content was not different between the groups. In $H_{1.0}$, the calculated concentrations of $K^+$ and $Na^+$ in the fluid which shifted into the intravascular space ($[K^+]sf$, $[Na^+]sf$) in the first 30 min after hemorrhage were higher in $[K^+]sf$ ($6.25 ± 0.70$ meq/l) and lower in $[Na^+]sf$ ($128.0 ± 3.2$ meq/l) than the pre-hemorrhage plasma level. With regard to $H_{1.0}$, $[K^+]sf$ and $[Na^+]sf$ were not different from the pre-hemorrhage level of plasma. These results suggest that α-adrenergic activation after hemorrhage induces $K^+$ movement into plasma to increase $[K^+]p$, which might be related to the fluid shift from the intracellular to the extracellular space.

Key words: potassium, sodium, blood volume, intracellular fluid, prazosin.

Acute hemorrhage induces an increase in the plasma level of $K^+$ ($[K^+]p$) [1–

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Hormones including catecholamines are known to play an important role in regulating the acute balance of K⁺ [4], and acute hemorrhage strongly increases the plasma levels of catecholamines proportionally to the level of hemorrhage [5] via sympato-adrenal activation, while the relationship between the sympato-adrenal activation and the increase in [K⁺]p after acute hemorrhage remains unknown.

Critz and Merrick [2] speculated that the increase in [K⁺]p after acute hemorrhage was the result of a fluid shift from intracellular space (ICS) into intravascular space (IVS). In addition, it has been reported that the fluid shift from ICS into IVS is important for the restoration of circulating blood volume (BV) after hemorrhage [6, 7].

From these studies, we speculated that sympato-adrenal activation after acute hemorrhage induces the shift of K⁺ from ICS into IVS to elevate [K⁺]p, which might be related to the fluid shift from ICS into IVS. To estimate the fluid shift and fluxes of K⁺ and Na⁺ from ICS into IVS, we measured changes in [K⁺]p, [Na⁺]p and BV continuously on nephrectomized rats during three levels of hemorrhage and the results were compared with hemorrhage after administration of the α₁-receptor antagonist prazosin.

METHODS

General preparations and surgical procedures. Experiments were performed on 36 male Wistar-Kyoto rats (260±8 g, mean±SE). Three or four days before the experiments, each rat underwent splenectomy under pentobarbital anesthesia. On the day of experiment, rats were anesthetized with an intraperitoneal injection of pentobarbital (5 mg/100 g body weight, Abbott, North Chicago, IL, USA), the trachea was incised and cannulated to ensure spontaneous respiration, and bilateral renal arteries and veins were ligated to avoid excretion of electrolytes and water.

The right common carotid artery and the right femoral vein were catheterized with polyethylene catheters (PE60 and PE50, Clay Adams, Parsippany, USA) to establish an extracorporeal arteriovenous shunt containing a glass coil in a well-type γ-counter (Osaka Dempo, Osaka, Japan) for measurement of BV and flow-through type glass electrodes (Horiba, Kyoto, Japan) for measurements of [Na⁺]p and [K⁺]p [8]. Concomitantly, catheters were placed in the right femoral artery and the right jugular vein which were connected to strain gauge transducers (P23XL, Gould, Oxnard, CA, USA) for measurement of systemic arterial pressure (AP) and central venous pressure (CVP), respectively. The left femoral artery was also catheterized for blood shedding and blood sampling. Sodium heparin (0.3 mg/100 g body weight, Kodama, Tokyo, Japan) was administered 1h after surgical preparation and 30 min after the start of extracorporeal circulation.

Experimental system, measurements and protocol. Continuous measurement of BV has been reported by Tanaka [9]. Briefly, 0.8 ml of 51Cr-tagged red cells from a donor rat were added to the extracorporeal circuit, and the radioactivity in

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blood was measured by the γ-counter in the extracorporeal circuit. The counts over each 30 s were corrected for background counts and stored in a microcomputer (PC9801U, NEC, Tokyo, Japan). BV was calculated as follows:

before hemorrhage

\[ V(t) = \frac{(V_1 \times C_i)}{C(t)} - V_{shunt} \]

- \( V(t) \): BV, ml
- \( V_1 \): injected BV, ml
- \( C_i \): radioactivity of the injected blood, counts/30 s
- \( C(t) \): radioactivity of the circulating blood, counts/30 s
- \( V_{shunt} \): volume in shunt, ml

after hemorrhage

\[ V'(t) = \frac{(V_1 \times C_i - V_H \times C_H)}{C(t)} - V_{shunt} \]

- \( V_H \): volume of shed blood, ml
- \( C_H \): radioactivity of shed blood, counts/30 s

\([\text{Na}^+]p\) and \([\text{K}^+]p\) were recorded on a chart recorder (Multi-Pen-Recorder, Rika Denki, Tokyo, Japan), and stored at 5-s intervals in the microcomputer. Data were averaged every 30 s, and the readings were calibrated using standard solutions and blood samples determined by flame photometry (Flame photometer 480, Corning, Medfield, Mass, USA).

AP and CVP were recorded on a chart recorder (Recti-Horitz-8K, NEC San-ei, Tokyo, Japan). Systolic and diastolic arterial pressure (SAP and DAP) were measured every 5 min, and the mean arterial pressure (MAP) was calculated as \( MAP = \frac{DAP + (SAP - DAP)}{3} \). Heart rate (HR) was counted every 5 min from the arterial wave on the chart recorder.

The blood flow in the extracorporeal circulation was maintained at 0.2 ml/min by a roller pump (Minipulse, Gilson, Villiers-le-bel, France). Body temperature was maintained at 37°C using a heat pad.

The radioactivity of \(^{51}\text{Cr}\)-tagged red cells in the extracorporeal shunt was measured, then the extracorporeal circulation was started. After stabilization of radioactivity, \([\text{Na}^+]p\), \([\text{K}^+]p\), AP and CVP, a 0.5-ml aliquot of blood was taken for determination of hematocrit (Hct, microcentrifuge), \([\text{Na}^+]p\) and \([\text{K}^+]p\). Twenty minutes before hemorrhage, saline or distilled water containing \(\alpha_1\)-adrenoceptor antagonist prazosin (0.2 mg/kg, Sigma, St. Louis, MO, USA) was administered in a volume of 0.5 ml. Levels of hemorrhage were defined as 0.5, 1.0 and 1.5% of body weight (body wt) for the saline-administered groups (H0.5, H1.0 and H1.5, respectively) and 1.0% of body wt for the prazosin-administered group (H1.0P). Hemorrhage was conducted over 5 min, and the shed blood was collected in a sample tube for determination of the radioactivity, Hct, \([\text{Na}^+]p\) and \([\text{K}^+]p\). All parameters were measured over a 60-min period after hemorrhage. At the end of the experiment, 0.5 ml of blood was also taken for determination of Hct, \([\text{Na}^+]p\) and \([\text{K}^+]p\).
For the determination of plasma K$^+$ and Na$^+$ contents, plasma volume (PV) calculated from BV and Hct, and [Na$^+$]p and [K$^+$]p were used. Hct was corrected for trapped plasma (0.96) and F-cell ratio (0.91). Changes in PV after hemorrhage were supposed to be proportional to those in BV because the red blood cell volume after hemorrhage in rats was constant during the course of the present study.

Statistics. Comparison between individual control values and experimental values were made by a one-way analysis of variance (ANOVA) and Fisher's least significant difference test. A one-way ANOVA for repeated measurements was used for comparison of data among H$_{0.5}$, H$_{1.0}$ and H$_{1.5}$ or between H$_{1.0}$ and H$_{1.0p}$, and subsequent post hoc tests to determine differences between means were performed using Fisher's least significant difference test [10]. All values are presented as means±SE, and the null hypothesis was rejected at $p<0.05$.

RESULTS

Baseline values obtained by averaging 10-min values for [K$^+$]p, [Na$^+$]p, BV, plasma K$^+$ and Na$^+$ contents, and hemodynamic parameters before the administration of saline or prazosin are summarized in Table 1. No parameters showed significant differences among H$_{0.5}$, H$_{1.0}$ and H$_{1.5}$ as well as between H$_{1.0}$ and H$_{1.0p}$.

Figure 1 illustrates changes in [K$^+$]p and [Na$^+$]p from the pre-hemorrhage values (Δ[K$^+$]p and Δ[Na$^+$]p). Infusion of saline or prazosin did not affect the levels of [K$^+$]p or [Na$^+$]p. [K$^+$]p increased significantly ($p<0.05$) from the pre-hemorrhage value at 8–10 min in H$_{0.5}$, 6–60 min in H$_{1.0}$, 6–60 min in H$_{1.5}$, and 8–10.5 min and 16–21 min in H$_{1.0p}$. The peak values of Δ[K$^+$]p were 0.18 meq/l at 8–10 min, 0.62 meq/l at 11.5–12.5 min, 1.64 meq/l at 14 min, and 0.25 meq/l at 18–18.5

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<tr>
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<th>H$_{0.5}$</th>
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<th>H$_{1.0p}$</th>
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<tr>
<td>[K$^+$]p (meq/l)</td>
<td>4.39±0.28</td>
<td>3.99±0.19</td>
<td>4.25±0.25</td>
<td>4.20±0.23</td>
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<td>[Na$^+$]p (meq/l)</td>
<td>137.9±1.2</td>
<td>141.0±2.1</td>
<td>138.7±0.8</td>
<td>137.0±1.1</td>
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<td>Plasma K$^+$ content (μeq/100 g·body wt)</td>
<td>13.64±1.33</td>
<td>13.69±1.61</td>
<td>12.89±0.95</td>
<td>13.97±1.33</td>
</tr>
<tr>
<td>Plasma Na$^+$ content (μeq/100 g·body wt)</td>
<td>419.7±13.1</td>
<td>431.8±31.6</td>
<td>423.9±17.1</td>
<td>475.8±26.2</td>
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<tr>
<td>BV (ml/100 g·body wt)</td>
<td>5.48±0.22</td>
<td>5.29±0.22</td>
<td>5.48±0.15</td>
<td>5.69±0.29</td>
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<tr>
<td>HR (beats/min)</td>
<td>414±15</td>
<td>412±16</td>
<td>425±20</td>
<td>397±26</td>
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<tr>
<td>MAP (mmHg)</td>
<td>120±4</td>
<td>116±6</td>
<td>114±4</td>
<td>123±4</td>
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<tr>
<td>CVP (mmHg)</td>
<td>−0.2±0.5</td>
<td>0.1±0.4</td>
<td>−0.2±0.5</td>
<td>0.6±0.7</td>
</tr>
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Values are means±SE of 9 rats for each experimental protocol. [K$^+$]p, plasma potassium concentration; [Na$^+$]p, plasma sodium concentration; BV, blood volume; HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure.

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min in H₀.5, H₁₀, H₁₅ and H₁₀p, respectively (Fig. 1A, C). Significant (p < 0.05) differences in Δ(K⁺)p were observed between H₀.5 and H₁₀ at 9–17 min, 23–32 min and 38–60 min, between H₀.5 and H₁₅ at 10.5–19.5 min, and between H₁₀ and H₁₅ at 11.5–18 min. Δ(K⁺)p in H₁₀ was significantly (p < 0.05) higher than that in H₁₀p at 10.5–15.5 min.

[Na⁺]p decreased significantly (p < 0.05) from the pre-hemorrhage value at 8–60 min in H₀.5, 13–60 min in H₁₀ and 8–60 min in H₁₅. In contrast, [Na⁺]p in H₁₀p increased (p < 0.05) from the pre-hemorrhage value at 53.5–60 min. The lowest values of H₀.5, H₁₀, H₁₅ were −1.0 meq/l at 11 min, −1.3 meq/l at 17 min and −3.5 meq/l at 16 min, respectively (Fig. 1B, D). Δ[Na⁺]p in H₁₅ was significantly (p < 0.05) lower than that in H₀.5 and H₁₀ at 13–60 min and 12–60 min, respectively. Δ[Na⁺]p in H₁₀ was significantly (p < 0.05) lower than that in H₁₀p at 14–20.5 min and 24–60 min.

Figure 2 illustrates changes in BV and in the percent recovery of BV with respect to the shed volume. Although ΔBV in H₀.5, H₁₀, H₁₅ and H₁₀p remained lower (p < 0.05) than the pre-hemorrhage value even at 60 min, BV in H₁₀p reached the pre-hemorrhage level at 38.5 min and increased significantly (p < 0.05) from the pre-hemorrhage value after 53 min. In H₀.5, H₁₀ and H₁₅, the percent recovery of BV was 46, 71, 25% at 60 min, respectively. ΔBV in H₁₀p was significantly (p < 0.05) higher than that in H₁₀ at 37–60 min.

Figure 3 shows changes in plasma K⁺ and Na⁺ contents (ΔK⁺ content and ΔNa⁺ content). Plasma K⁺ and Na⁺ contents remained unchanged after administration of saline and prazosin in all groups. After hemorrhage, plasma K⁺ content increased significantly (p < 0.05) from the post-hemorrhage value at 10–12 and 25–60 min in H₀.5, at 6–60 min in H₁₀, at 8.5–60 min in H₁₅ and at 7–60 min in H₁₀p (Fig. 3A, C). There were no differences in ΔK⁺ content between H₁₀ and H₁₀p.

Plasma Na⁺ content also increased significantly (p < 0.05) from the post-hemorrhage value at 25.5–60 min in H₀.5, at 8.5–60 min in H₁₀, at 19–60 min in H₁₅ and at 8–60 min in H₁₀p (Fig. 3B, D). ΔNa⁺ content in H₁₀p was significantly (p < 0.05) higher than that in H₁₀ at 37–60 min.

Changes in HR, MAP and CVP from the pre-hemorrhage value (ΔHR, ΔMAP and ΔCVP) are illustrated in Figs. 4 and 5. Administration of prazosin increased (p < 0.05) HR by 12 beats/min (Fig. 5A) and decreased (p < 0.05) MAP and CVP by 19 and 0.6 mmHg, respectively (Fig. 5B, C). Although HR increased significantly (p < 0.05) after hemorrhage in H₀.5, H₁₀ and H₁₅ (Fig. 4A), HR in H₁₀p remained constant until 20 min (Fig. 5A). MAP and CVP decreased significantly (p < 0.05) after hemorrhage in each group. Significant (p < 0.05) differences in ΔHR were observed between H₀.5 and H₁₅ and between H₁₀ and H₁₅ at 45–60 min. ΔMAP was different (p < 0.05) among groups only at 5 and 10 min. Significant (p < 0.05) differences in ΔCVP were observed between H₀.5 and H₁₅ at 5–10 min and 30–60 min and between H₁₀ and H₁₅ at 5 min and 30–60 min. Both ΔMAP and ΔCVP were lower (p < 0.05) in H₁₀p than H₁₀ throughout the experiment.

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Fig. 1. Changes in plasma concentrations of \(K^+\) (\(\Delta[K^+]p\)) and \(Na^+\) (\(\Delta[Na^+]p\)) after hemorrhage at three different levels (A, B) and under administration of prazosin (C, D). Hemorrhage was conducted from 0 to 5 min. Values are means ± SE for 9 rats. \(H_{0.5}\), \(H_{1.0}\) and \(H_{1.5}\): hemorrhage at the level of 0.5, 1.0 and 1.5% of body wt, respectively. \(H_{1.0p}\): hemorrhage at the level of 1.0% of body wt under administration of prazosin. *Significant differences between \(H_{1.0}\) and \(H_{1.0p}\).
Fig. 2. Changes in blood volume (ΔBV, A, C) and percent recovery of BV with respect to the shed volume (B, D) after hemorrhage. Values are means ± SE for 9 rats. *Significant differences in BV between $H_{t0}$ and $H_{t0, \text{pre}}$. 

Plasma K⁺ after hemorrhage.
Fig. 3. Changes in K\(^+\) and Na\(^+\) content in plasma (\(\Delta K^+\) content and \(\Delta Na^+\) content) after hemorrhage. Values are means ± SE for 9 rats. *Significant differences between H\(_{1.0}\) and H\(_{1.0p}\).
Fig. 4. Changes in heart rate, mean arterial pressure and central venous pressure ($\Delta HR$, $\Delta MAP$ and $\Delta CVP$, respectively) in $H_{0.5}$, $H_{1.0}$ and $H_{1.5}$. Values are means±SE for 9 rats.

To estimate the concentrations of $K^+$ and $Na^+$ in the fluid shifted into the IVS after hemorrhage ($[K^+]_{sf}$ and $[Na^+]_{sf}$), we divided the net increase in plasma $K^+$ and $Na^+$ content over the first and second 30-min periods during the 1-h observation after hemorrhage by the net increase in PV (equal to the increase in BV) at the
Fig. 5. Changes in heart rate, mean arterial pressure and central venous pressure in $H_{1.0}$ and $H_{1.0p}$. Values are means±SE for 9 rats. *Significant differences between $H_{1.0}$ and $H_{1.0p}$.

There were no differences in $[K^+]_{sf}$ among $H_{0.5}$, $H_{1.0}$ and $H_{1.5}$ in the first and second 30-min periods after hemorrhage. However, $[K^+]_{sf}$ in $H_{1.0p}$ was lower ($p<0.05$) than that in $H_{1.0}$ in the first 30 min after hemorrhage (Fig. 6A). Although $[K^+]_{sf}$ in the first 30 min was greater ($p<0.05$) than the
Fig. 6. Calculated concentrations of $K^+$ and $Na^+$ in the shifted fluid ($[K^+]_{sf}$ and $[Na^+]_{sf}$) in both 30-min periods during the 1h observation period after hemorrhage. The variable was obtained from the net increase in BV and plasma $K^+$ and $Na^+$ contents. Values are means±SE for 9 rats. *Significant differences between $H_{1.0}$ and $H_{1.0p}$. †Significant differences from the pre-hemorrhage value of $[K^+]_p$ or $[Na^+]_p$.

Pre-hemorrhage values of $[K^+]_p$ in $H_{0.5}$, $H_{1.0}$ and $H_{1.5}$ (shown in Table 1), there were no significant differences in both the first and the second 30-min values in $H_{1.0p}$ from the pre-hemorrhage value of $[K^+]_p$.

$[Na^+]_{sf}$ in $H_{1.5}$ was significantly ($p<0.05$) lower than that in $H_{1.0}$ in the first 30 min, and $[Na^+]_{sf}$ in $H_{1.0}$ was significantly ($p<0.05$) greater than those in $H_{0.5}$ and $H_{1.5}$ in the second 30 min (Fig. 6B). $[Na^+]_{sf}$ in $H_{1.0}$ was significantly ($p<0.05$) lower than that in $H_{1.0p}$ only in the first 30 min. $[Na^+]_{sf}$ in $H_{0.5}$, $H_{1.0}$ and $H_{1.5}$
decreased significantly ($p < 0.05$) in the first 30 min from the pre-hemorrhage values of $[Na^+]_p$.

DISCUSSION

The present study demonstrates that $\alpha$-adrenergic activation after acute hemorrhage increases $[K^+]_p$, which is attributable to the influx of fluid from ICS into IVS.

Anderson and Shoemaker reported in their experiment on anesthetized dogs that hemorrhage of about 20% of BV induced an immediate increase in $[K^+]_p$ [1]. In addition, Critz and Merrick showed that hemorrhage ranging 10–30% of BV in rabbits induced a prolonged increase in $[K^+]_p$ which continued until 24 h–7 days after hemorrhage [2]. However, it is debatable whether the increase in $[K^+]_p$ indicates a net increase in influx of $K^+$ from ICS into IVS because the plasma $K^+$ content was not measured in these experiments. In the present study, the plasma $K^+$ content in $H_{0.5}$, $H_{1.0}$ and $H_{1.5}$ increased immediately after hemorrhage, then decreased by 47.7, 27.6 and 64.6% of the peak value in $H_{0.5}$, $H_{1.0}$ and $H_{1.5}$, respectively, and increased again gradually (Fig. 3A). It is noteworthy that continuous determinations of $[K^+]_p$, $[Na^+]_p$ and BV in this experiment made it possible to detect small changes in these variables and also plasma $K^+$ content.

The acute balance of $[K^+]_p$ is regulated by extrarenal mechanisms [4], and catecholamines are known to modify $[K^+]_p$. Infusion of epinephrine or norepinephrine induces a transient increase in $[K^+]_p$ via $\alpha$-adrenoceptors, and epinephrine is related to the subsequent uptake of $K^+$ into muscles mediated via $\beta$-adrenoceptors [4, 11, 12]. Changes in acid-base balance also affect $[K^+]_p$ [4, 13]. Hemorrhage potentially activates the sympatho-adrenal system, and the magnitude of the catecholamine response is related to the level of hemorrhage [5]. Prazosin is a potent postsynaptic adrenergic ($\alpha_1$)-receptor antagonist. Hemorrhage under administration of prazosin suppressed the transient increase in $[K^+]_p$ by 59.7% at the peak value (Fig. 1C). In contrast to the higher $[K^+]_p$ in $H_{1.0}$ than the pre-hemorrhage value of $[K^+]_p$ in the first 30 min after hemorrhage, $[K^+]_p$ in $H_{1.0}$ retained the same level as the pre-hemorrhage value of $[K^+]_p$ throughout the experiment (Fig. 6A). These results suggest that the increases in $[K^+]_p$ observed in $H_{0.5}$, $H_{1.0}$ and $H_{1.5}$ were the result of influx of $K^+$ from ICS into IVS via $\alpha$-adrenergic activation after hemorrhage.

Prazosin suppressed the decrease in $[Na^+]_p$ after hemorrhage (Fig. 1D). While the plasma $Na^+$ content was not significantly different between $H_{1.0}$ and $H_{1.0P}$ within 35 min after hemorrhage (Fig. 3D), $[Na^+]_p$ in $H_{1.0P}$ was at the same level as the pre-hemorrhage level of $[Na^+]_p$ in the first 30 min after hemorrhage (Fig. 6B). The results suggest that $\alpha$-adrenergic activation is related to the net inward movement of fluid with a lower $Na^+$ concentration than in plasma into IVS.

In the present study, the levels of catecholamines were not measured. However, HR is known to reflect sympahto-adrenal activity [14–16]. In $H_{0.5}$, $H_{1.0}$ and

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H₁₅, HR increased after hemorrhage, and the increase was sustained to the end of experiment with significant differences between the groups (Fig. 4A), which suggests that the increase in sympatho-adrenal activity is proportional to the level of hemorrhage. In contrast, prazosin suppressed the immediate response of HR after hemorrhage (Fig. 5A). The reasons for the greater HR before hemorrhage and the late increase in HR in H₁ₒ Kohana remain unknown. A prolonged decrease in MAP and CVP (Fig. 5B, C) which would activate baroreceptors [17] might induce an increase in the plasma level of epinephrine, which increased HR via β-adrenoceptors.

Acid-base balance also modifies [K\(^+\)]p; it is well known that acidosis increases [K\(^+\)]p and alkalosis decreases [K\(^+\)]p [4, 13]. It was reported that hemorrhagic hypotension in anesthetized cats induced respiratory alkalosis rather than metabolic acidosis [18]. In our preliminary study, pH, pCO₂ and base excess did not change after hemorrhage of 10% body wt with or without administration of prazosin. Thus, the increase in [K\(^+\)]p could not be attributed to the acid-base balance.

Pirkle and Gann suggested by mathematical modeling that fluid movement occurred from ICS into IVS after hemorrhage [19]. Itoh et al., using the tracer method, showed that the fluid movement from ICS played an important role in the restoration of BV after dehydration [6]. The net influx of fluid with a lower Na\(^+\) concentration than in plasma after hemorrhage in the present study strongly supports these reports, and the influx of K\(^+\) might be related to the fluid shift from ICS. However, in the present study, K\(^+\) movement was not directly linked with fluid movement. Anderson and Shoemaker showed that the released K\(^+\) originated largely from hepatocytes from the measurements of [K\(^+\)]p and blood flow rate in the hepatic vein after hemorrhage in dogs [1]. Augmented glycogenolysis also occurs in liver after hemorrhage [20]. The simultaneous release of K\(^+\) and glucose into the extravascular space after infusion of α-adrenoceptor agonist phenylephrine was shown in the perfused rat liver [21]. Järhult proposed that the driving force for the fluid movement from ICS after hemorrhage was osmosis due to hyperglycemia, and that the fluid originated largely from muscle [7]. These studies suggest that the increase in [K\(^+\)]p is indirectly linked to the fluid shift from ICS. In contrast, Hirose [22] and Moreno et al. [23] reported the possibility of simultaneous movement of K\(^+\) and water during infusion of hypertonic and isotonc mannitol.

Although α-adrenergic activation was supposed to induce the fluid shift from ICS in the present study, the restoration of BV in H₁ₒ Kohana was greater than that in H₁₀ (Fig. 2C). The fluid movement between IVS and the interstitial space (ISS) is determined by Starling forces. The administration of prazosin attenuated the recovery of MAP after hemorrhage. The results might indicate lower perfusion pressure in capillary vessels, which enhanced influx of the interstitial fluid into IVS. The decrease in capillary pressure after hemorrhage is supposed to be caused by an increase in the pre-/postcapillary resistance ratio due to the higher β-adrenergic dilator influence in post- than in pre-capillary vessels interacting with the concom-

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itant α-adrenergic constrictor response [24, 25]. Administration of prazosin might relatively enhance the β-adrenergic dilatory effect on the postcapillary sphincter to induce greater recovery of BV. In addition, Morimoto reported that the fluid distribution between ISS and IVS was determined by differences in compliance between ISS and IVS [26]. Hemorrhage would decrease vascular compliance via sympatho-adrenal activation [27]. The prolonged decrease in CVP in H1,0P despite enhanced restoration of BV would be related to loss of this compensation mechanism.

In summary, [K+]p increased with decreases in [Na+]p after hemorrhage in proportion to the level of hemorrhage. The change was attributed to net influx of fluid with higher K+ and lower Na+ concentrations than in plasma from ICS into IVS. α-adrenergic activation after hemorrhage was suggested to be involved in the elevation of [K+]p and blood volume recovery.

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