ANALYTICAL STUDIES ON CHANGES IN ARTERIAL AND VENOUS OSMOLALITIES INDUCED BY ACUTE HEMORRHAGIC HYPOTENSION IN DOGS

TOYOHISA SUGIYAMA

There are many papers on the studies of metabolic changes in the peripheral tissue in shock. Concerning plasma osmolality\(^1\)\(^-\)\(^4\) it is described that the plasma osmolality of the arterial blood was markedly increased in dogs or cats with hemorrhagic hypotension, and that the increased plasma glucose was mainly responsible for it, and it is also postulated that hyperosmolality of the arterial plasma would cause a transcapillary osmotic fluid absorption from the extravascular space of the skeletal muscle into the circulatory system to increase the plasma volume.

On the other hand, it was reported by Hayase et al\(^5\)\(^-\)\(^6\) that plasma osmolality is more increased in venous blood than in arterial blood in dogs with acute hemorrhagic hypotension.

The present paper describes the results of a study in which the variation of arterial and venous plasma osmolalities and osmotically active substances in the dog hindlimbs induced by blood depletion were measured with references to the significance of the effects of respiratory volume and blood flow through sampling sites.

Key Words:
- Hemorrhagic hypotension
- Plasma osmolality
- Osmotically active substance
- Ventilation volume
- Peripheral blood flow

METHOD

Mongrel dogs, weighing 8–22 kg, were anesthetized with sodium pentobarbital (25–30 mg/kg), and intubated endotracheally. A local circuit of extracorporeal circulation was provided in the right femoral artery. An electromagnetic flowmeter (MF-2, Nihon Kohden Co., Ltd.) was inserted into this circuit in order to measure blood inflow, and a side arm was provided in the circuit so as to measure the perfusion pressure with an electromanometer (MP-24T, Nihon Kohden Co., Ltd.). Blood samples were collected from the right femoral artery and vein. The dogs were depleted of blood, from the left carotid artery, during the period of more than five minutes, until a mean blood pressure (MBP) of 60 mmHg was achieved (with a mean blood loss of 20ml/kg). All dogs were infused intravenously with 10,000 IU of heparin.

1) Alterations in the osmolal arterio-venous difference (Osm A-V) with blood depletion

Two blood samples were collected simultaneously from the femoral artery and vein of dogs under spontaneous respiration at 20 minutes intervals for use as control samples; and each dog was then depleted of blood, until a MBP of 60 mmHg was achieved. Blood samples were collected from the artery and the vein, 10 and 20 minutes after the beginning of blood depletion.

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On all experimental dogs, blood was transfused to restore the normal blood pressure, and blood depletion was resumed in the same way about 60 minutes later.

In order to examine whether the sympathetic nervous system would be influential on alterations in Osm A-V with blood depletion, in some cases the sciatic nerve was severed at the level of the ischial tuberosity, also, the femoral nerve at the level of the femoral triangle, one hour before blood depletion.

Each blood sample was centrifuged at 2,000 r.p.m. for 20 minutes, and the plasma osmolality was measured on 2.5 ml of plasma with the Fiske osmometer (the model No. G-62) in triplicates, the mean value was used as plasma osmolality.

2) Relationship between ventilation volume and Osm A-V

Hyperventilation was observed in hypotensive dog induced by blood depletion. In order to examine this phenomenon, the dogs were given succinylcholine without blood depletion, and placed under the controlled ventilation volumes of 160, 400 and 800 ml/min/kg for 15 minutes, and the plasma osmolalities and HCO₃⁻ (Blood Gas Analyzer BMS 3, PHM72) levels in the femoral artery and vein were measured. In the present experiment, the thorax of each animal was perforated, so that the pressure around the lungs would always be equal with the atmospheric pressure.

3) Osm A-V and osmoactive substances in blood depletion under constant ventilation

Each dog was given succinylcholine, and depleted of blood 30 minutes later under controlled ventilation which was maintained at 250 ml/min/kg, until a MBP of 60 mmHg was achieved. Blood samples were collected simultaneously from the femoral artery and vein in the control stage and also 15, 30 and 60 minutes after the beginning of blood depletion. Each sample was analyzed for osmolality and HCO₃⁻ and also for sodium, potassium, chloride and glucose (Technichon, SMA 6/60).

4) Local blood flow and Osm A-V

i) Blood depletion experiments under controlled local blood flow

Blood flow through the right femoral artery was maintained constantly by use of flow pump (C-16, Tokyo Rikakikai Co., Ltd.) and electromagnetic flowmeter. The animals were placed under spontaneous respiration for about 15 minutes, and blood samples were then collected simultaneously from three sites, i.e. the right femoral artery and vein and the left femoral vein twice at an interval of 20 minutes; the data so obtained were used as control. The animals were then depleted of blood by the aforementioned method, until a MBP of 60 mmHg was attained, and blood samples were likewise collected 10 and 20 minutes after the beginning of blood depletion. During this experiment, the blood flow in the right femoral artery was maintained equally to the control.

ii) Decrease in local blood flow

Blood samples were collected from the right femoral artery and vein twice at an interval of 20 minutes for use as control samples. The right femoral artery of each animal was then clamped to decrease the blood flow in this artery to one fifth (1/5) of the control flow, and blood samples were collected 10 and 20 minutes later.

5) Osm A-V in the right and left hindlimbs in blood depletion

Blood samples were collected simultaneously from three sites, i.e. the right femoral artery and vein, and left femoral vein twice at an interval of

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Fig.1. Two typical examples showing alterations in plasma osmolality in the femoral artery and vein with hemorrhage. For details, refer to Result 1).

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TABLE I  EFFECTS OF HEMORRHAGIC HYPOTENSION ON OSMOLAL A-V DIFFERENCE

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td><strong>Osm A</strong></td>
<td>297.6 ± 1.7</td>
<td>296.9 ± 1.5</td>
</tr>
<tr>
<td><strong>Osm V</strong></td>
<td>297.4 ± 1.6</td>
<td>297.0 ± 1.5</td>
</tr>
<tr>
<td><strong>Osm A-V</strong></td>
<td>+0.3 ± 0.2</td>
<td>-0.1 ± 0.2</td>
</tr>
<tr>
<td><strong>MBP</strong></td>
<td>126 ± 6</td>
<td>118 ± 5</td>
</tr>
<tr>
<td><strong>Fem. Flow</strong></td>
<td>4.0 ± 0.6</td>
<td>3.5 ± 0.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td><strong>Osm A</strong></td>
<td>302.3 ± 2.5</td>
<td>302.1 ± 2.4</td>
</tr>
<tr>
<td><strong>Osm V</strong></td>
<td>304.5 ± 2.2</td>
<td>304.0 ± 2.2</td>
</tr>
<tr>
<td><strong>Osm A-V</strong></td>
<td>-2.1 ± 0.6</td>
<td>-2.0 ± 0.3</td>
</tr>
<tr>
<td><strong>MBP</strong></td>
<td>116 ± 8</td>
<td>111 ± 11</td>
</tr>
<tr>
<td><strong>Fem. Flow</strong></td>
<td>1.6 ± 0.3</td>
<td>1.4 ± 0.3</td>
</tr>
</tbody>
</table>

* Significant difference from the Control-I, p < 0.01.

Osm A: femoral artery plasma osmolality (mOsm/kgH₂O)
Osm V: femoral venous plasma osmolality (mOsm/kgH₂O)
Osm A-V: osmolal arterio-venous difference (mOsm/kgH₂O)
MBP: mean blood pressure (mmHg)
Fem. Flow: femoral artery flow (ml/min/kg)
I: 20 min. before hemorrhage. II: immediately before hemorrhage. III: 10 min. after the beginning of hemorrhage. IV: 20 min. after the beginning of hemorrhage.

10 minutes for use as control samples. The animals were then depleted of blood about five minutes over until a MBP of 60 mmHg was reached, blood samples were collected at an interval of ten minutes for one hour to measure the plasma osmolality.

RESULTS

1) Alterations in Osm A-V with blood depletion

In many of 11 experimental dogs, the control Osm A-V was mostly 0 mOsm/kg H₂O as shown in Example-1 of Fig.1. In these animals, the Osm A-V shifted toward the negative side after blood depletion. On blood transfusion that followed the blood depletion, the Osm A-V returned close to 0 mOsm/kg H₂O, but on re-depletion of blood, the Osm A-V shifted again toward the negative side; thus, a very good reproducibility was obtained. In animals whose control Osm A-V were strongly negative as given in Example 2 of Fig.1, blood depletion was followed by no further shifting of the Osm A-V toward the negative side. However, after the Osm A-V restored the positive value on blood transfusion, the Osm A-V shifted again toward the negative side on re-depletion of blood.

In view of these findings, the experimental animals were divided into a group with the control Osm A-V on the positive side of −1.0 mOsm/kg H₂O (Group A) and a group with the control Osm A-V on the negative side of −1.0 mOsm/kg H₂O (Group B) (Table I). The control Osm A-V of Group A (N = 15) was +0.3 mOsm/kg H₂O (20 min. before blood depletion) and −0.1 mOsm/kg H₂O (immediately before blood depletion), and the Osm A-V 10 min. after the beginning of blood depletion was −1.5 mOsm/kg.
TABLE II  EFFECTS OF HEMORRAGIC HYPOTENSION IN HINDLIMBS WITH ACUTE SCIATIC AND FEMORAL NERVE SECTION

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Osm A</td>
<td>301.1 ± 2.0</td>
<td>300.9 ± 1.9</td>
</tr>
<tr>
<td>Osm V</td>
<td>301.0 ± 2.0</td>
<td>300.6 ± 1.8</td>
</tr>
<tr>
<td>Osm A-V</td>
<td>+0.1 ± 0.1</td>
<td>+0.3 ± 0.2</td>
</tr>
</tbody>
</table>

* Significant difference from the Control-I, p < 0.01. Abbreviations as in Table I.

H₂O and that 20 min. after the beginning of blood depletion, -2.2 mOsm/kg H₂O. There was no difference of MBP between the two groups, but in group B the blood flow of the femoral artery was apparently less than that in group A concerning the amount of flow at the control stage (p < 0.05). In all the subsequent experiments, animals whose control Osm A-V was on the negative side of -1.0 mOsm/kg H₂O were excluded in order to obtain homogeneity in the data.

Blood depletion experiments were likewise made under the condition that the sciatic nerve and femoral nerve that include the most part of the sympathetic vasomotor nerve were severed (Table II). The control Osm A-V was +0.1 and +0.3 mOsm/kg H₂O, 10 and 20 min. after the beginning of blood depletion, respectively. Thus, the negative shift of Osm A-V with hemorrhagic hypotension was retained even when the sympathetic nerve was severed.

2) Effects of ventilation volume on Osm A-V
As described in Method 2), the ventilation volume was altered in three steps to compare the Osm A-V (N = 5) (Fig. 2). The MBP decreased with the increase of ventilation volume, but remained over 90 ± 10 mmHg throughout the experiment. The plasma osmolalities and HCO₃⁻ levels in both the artery and the vein decreased with the increase of ventilation volume, and in these parameters the alterations of the arterial blood were particularly striking; therefore, both the Osm A-V and the HCO₃⁻ A-V shifted toward the negative side (Osm A-V: p < 0.1, HCO₃⁻ A-V: P < 0.05). In other words, the negative shift of Osm A-V in this instance appears mainly dependent on the negative shift of HCO₃⁻ A-V.

3) Blood depletion experiments under constant mechanical ventilation
TABLE III  CHEMICAL COMPOSITION OF ARTERIAL AND VENOUS BLOOD PLASMA BEFORE AND DURING THE HEMORRHAGIC HYPOTENSION AT CONSTANT MECHANICAL VENTILATION

(N = 5)  Mean ± SE

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>After the beginning of hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>15 min</td>
</tr>
<tr>
<td>MBP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mmHg</td>
<td>144 ± 3</td>
<td>*66 ± 2</td>
</tr>
<tr>
<td>mOsm/kgH₂O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osm A</td>
<td>296.2 ± 1.4</td>
<td>297.7 ±</td>
</tr>
<tr>
<td>Osm V</td>
<td>296.7 ± 1.4</td>
<td>300.1 ±</td>
</tr>
<tr>
<td>Osm A-V</td>
<td>-0.5 ± 0.3</td>
<td>*2.4 ± 0.4</td>
</tr>
<tr>
<td>mEq/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCO₃ A</td>
<td>21.9 ± 1.4</td>
<td>18.8 ± 1.3</td>
</tr>
<tr>
<td>HCO₃ V</td>
<td>22.7 ± 1.6</td>
<td>22.4 ± 1.2</td>
</tr>
<tr>
<td>HCO₃ A-V</td>
<td>-0.8 ± 0.2</td>
<td>*3.6 ± 0.3</td>
</tr>
<tr>
<td>MEq/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na A</td>
<td>144.5 ± 1.0</td>
<td>143.0 ± 1.8</td>
</tr>
<tr>
<td>Na V</td>
<td>144.8 ± 1.1</td>
<td>144.5 ± 1.0</td>
</tr>
<tr>
<td>Na A-V</td>
<td>-0.3 ± 0.3</td>
<td>-1.5 ± 0.8</td>
</tr>
<tr>
<td>mEq/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K A</td>
<td>3.8 ± 0.3</td>
<td>4.5 ± 0.3</td>
</tr>
<tr>
<td>K V</td>
<td>3.9 ± 0.3</td>
<td>4.5 ± 0.5</td>
</tr>
<tr>
<td>K A-V</td>
<td>-0.1 ± 0.0</td>
<td>0 ± 0.4</td>
</tr>
<tr>
<td>mEq/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl A</td>
<td>104.8 ± 0.8</td>
<td>107.0 ± 0.6</td>
</tr>
<tr>
<td>Cl V</td>
<td>104.3 ± 0.4</td>
<td>104.8 ± 0.9</td>
</tr>
<tr>
<td>Cl A-V</td>
<td>+0.5 ± 0.5</td>
<td>+2.2 ± 0.7</td>
</tr>
<tr>
<td>mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose A</td>
<td>120 ± 4</td>
<td>148 ± 19</td>
</tr>
<tr>
<td>Glucose V</td>
<td>118 ± 5</td>
<td>120 ± 9</td>
</tr>
<tr>
<td>Glucose A-V</td>
<td>+2 ± 1</td>
<td>+28 ± 10</td>
</tr>
</tbody>
</table>

* Significant difference from the control value, P < 0.01.
** Significant difference from the control value, 0.01 < P < 0.05

(250 ml/min/kg)

The findings in five dogs are given in Table III. Both the plasma osmolality in the artery and in the vein were elevated, in particular the one of the venous blood was markedly elevated. Therefore, the Osm A-V shifted progressively toward the negative side for one hour (P < 0.02). Alterations in the main osmoactive substance levels were such, that the HCO₃ A-V and the Na A-V shifted toward the negative side, while the Cl A-V and the glucose A-V shifted toward the positive side. 4) Local blood flow and Osm A-V i) Blood depletion experiments under controlled local blood flow

In five dogs, the blood flow in the right femoral artery was maintained at the same level as the control blood flow even after blood depletion as described in Method 4). As given in Table IV, the negative shift of Osm A-V in the hindlimb, whose inflow was maintained at the same level as the control flow even after blood

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TABLE IV  EFFECTS OF FEMORAL ARTERY FLOW ON OSMOLAL A-V DIFFERENCE DURING HEMORRHAGE

N = 5  Mean ± SE

<table>
<thead>
<tr>
<th></th>
<th>Natural inflow (left hindlimb)</th>
<th></th>
<th>Hemorrhage</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>Osm A</td>
<td>300.1 ± 1.8</td>
<td>300.5 ± 2.1</td>
<td>300.1 ± 2.2</td>
<td>303.0 ± 3.2</td>
</tr>
<tr>
<td>Osm V</td>
<td>300.5 ± 1.8</td>
<td>300.5 ± 1.5</td>
<td>302.7 ± 2.1</td>
<td>306.0 ± 2.5</td>
</tr>
<tr>
<td>Osm A-V</td>
<td>−0.4 ± 0.4</td>
<td>0 ± 0.7</td>
<td>*−2.5 ± 0.8</td>
<td>*−3.0 ± 1.3</td>
</tr>
</tbody>
</table>

Constant inflow equal to the control value (right hindlimb)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Control</th>
<th>Hemorrhage</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>Osm A</td>
<td>300.1 ± 1.8</td>
<td>300.5 ± 2.1</td>
<td>300.1 ± 2.2</td>
<td>303.0 ± 3.2</td>
</tr>
<tr>
<td>Osm V</td>
<td>300.5 ± 1.7</td>
<td>300.4 ± 1.7</td>
<td>301.4 ± 2.0</td>
<td>304.2 ± 3.0</td>
</tr>
<tr>
<td>Osm A-V</td>
<td>−0.3 ± 0.2</td>
<td>+0.1 ± 0.6</td>
<td>**−1.2 ± 0.6</td>
<td>**−1.2 ± 0.9</td>
</tr>
</tbody>
</table>

* Significant difference from the Control-I,  P < 0.1
** Significant difference from the Control-I,  P < 0.3
Abbreviations as in Table I.

TABLE V  EFFECTS OF FLOW REDUCTION FOLLOWING MECHANICAL ARTERIAL OBSTRUCTION ON OSMOLAL A-V DIFFERENCE

N = 4  Mean ± SE

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th></th>
<th>Clamping</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>Osm A</td>
<td>298.6 ± 2.8</td>
<td>298.9 ± 2.7</td>
<td>298.7 ± 2.3</td>
<td>299.3 ± 2.1</td>
</tr>
<tr>
<td>Osm V</td>
<td>299.0 ± 2.7</td>
<td>299.0 ± 2.6</td>
<td>299.6 ± 2.4</td>
<td>298.6 ± 2.1</td>
</tr>
<tr>
<td>Osm A-V</td>
<td>−0.5 ± 0.2</td>
<td>−0.1 ± 0.3</td>
<td>−0.9 ± 0.4</td>
<td>+0.7 ± 0.5</td>
</tr>
</tbody>
</table>

1: 20 min. before the clamping of the femoral artery.
II: immediately before the clamping of the femoral artery.
III: 10 min. after the clamping of the femoral artery.
IV: 20 min. after the clamping of the femoral artery.

depletion, was diminished as compared with the one of the other side.

ii) Decrease in local blood flow

In four dogs, the blood flow in the right femoral artery was decreased to one fifth (1/5) of the control flow as described in Method 4) ii). As shown in Table V, in the decrease of the local blood flow without blood depletion, the Osm A-V shift toward the negative side was not observed.

5) Observation of Osm A-V in right and left hindlimbs in blood depletion

The effects of hemorrhagic hypotension on the Osm A-V of the femoral artery and that of the femoral vein on both side were observed for one hour as described in Method 5). As given in the bottom section of Fig. 3, the MBP was maintained at about 60 mmHg. The plasma osmolality, as shown in the top section of Fig. 3, increased gradually in both the artery and the vein after blood depletion, and this tendency was particularly marked in the vein. Therefore, the
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Osm A-V in the hindlimb on both side, as shown in the middle part of Fig. 3, shifted toward the negative side for about one hour (N = 4).

**DISCUSSION**

Two incompatible studies with osmolar arteriovenous difference in acute hemorrhagic hypotension were reported. Järhult\(^5\)-\(^6\) depleted cats of blood to a MBP of 50 mmHg under spontaneous respiration, and found that the Osm A-V of the thigh muscle shifted toward the positive side. That is, the mean control Osm A-V was -1.0 mOsm/kg H\(_2\)O, while the mean Osm A-V 20 minutes after blood depletion was +12.0 mOsm/kg H\(_2\)O. On this instance, the mean glucose A-V was +120 mg/dl (equivalent to an osmolality of about 7 mOsm/kg H\(_2\)O); hence, the positive shifting of Osm A-V was mainly attributable to elevated glucose concentration. On the other hand, Hayase et al\(^5\)-\(^6\) depleted dogs of blood until a MBP 60 mmHg under spontaneous respiration, and found that the Osm A-V of hindlimb shifted toward the negative side. That is, the mean control Osm A-V was -0.4 mOsm/kg H\(_2\)O, while the mean Osm A-V 30 minutes after blood depletion was -2.7 mOsm/kg H\(_2\)O. On this instance, the mean glucose A-V was +14 mg/dl (+0.8 mOsm/kg H\(_2\)O). Hayase et al\(^5\)-\(^6\) suggested that the negative shifting of Osm A-V with blood depletion was caused by the negative shifting of HCO\(_3\) \(^-\) A-V and Na A-V exceed the positive shifting of glucose A-V and Cl A-V. The author discussed the mechanisms of negative shifting of Osm A-V with blood depletion concerning to local sympathetic nerve, respiration and local blood flow.

For preliminary experiment, the control value of plasma osmolality was examined. As given in Table I, in group A whose control Osm A-V was on the positive side of -1.0 mOsm/kg H\(_2\)O, with the blood depletion the Osm A-V was shifted toward the negative side of -1.0 mOsm/kg H\(_2\)O. On the other hand, in group B whose control Osm A-V on the negative side of -1.0 mOsm/kg H\(_2\)O, no further shift was observed. As mentioned in result I), in the group B the blood flow of the femoral artery was apparently less than that in group A concerning the amount of flow at the control stage. Therefore, it was appeared that dogs in group B were in poor condition at the control stage.

Plasma HCO\(_3\), which was main substance of plasma osmolality, was significantly affected by respiration. Hyperventilation was observed in hypotensive dogs induced by blood depletion, for that reason the relationship between ventilation volume and Osm A-V were examined. As given in Fig. 2, both Osm A-V and HCO\(_3\) A-V shifted toward the more negative side, according to the increase of ventilation volume. In this experiment plasma osmolality decreased with the increase of ventilation volume. The decreased plasma osmolality was derived from the decreased HCO\(_3\) in arterial blood, which was exhaled as CO\(_2\) from the lung alveoli. However, as given in Table III, Osm A-V shifted toward the negative side even in blood depletion with a constant ventilation volume of 250 ml/min/kg. In this experiment, the Na A-V and HCO\(_3\) A-V shifted toward the negative side, but the glucose A-V and Cl A-V toward the positive side. It was Na and HCO\(_3\) that were mainly responsible for the negative shifting of Osm A-V. Increased plasma osmolality with hemorrhagic hypotension was probably caused by the increased Na, Cl, glucose, lactate, pyruvate and other elements. From these findings, it can be considered that the negative shifting of the Osm A-V in hemorrhagic hypotension is derived not only from the
release of $\text{HCO}_3^-$ by the lungs through hyperventilation, but also from the release of $\text{HCO}_3$ and Na by peripheral tissue. In these experiments, $\text{HCO}_3$ levels were measured in an air tight condition, while the osmolalities in an air equilibrium condition. $\text{HCO}_3$ A-V levels in air tight and air equilibrium condition were measured on the same sample, without large difference between them. The chloride shift suggest that the chloride diffused from the plasma into the red blood cells at peripheral blood vessels.

In the femoral artery at a MBP of 60 mmHg, the blood flow from the control level decreased to one third (1/3) and one fifth (1/5). In order to examine the effects of this decrease in blood flow, the blood flow in the femoral artery on one side was maintained at the same level as the control even after blood depletion (Table IV). The negative shift of the Osm A-V after blood depletion was apparently reduced, as compared with that on the other side. An increased blood flow with dilution may be considered for it. Also in order to study if the decrease only in local blood flow would shift the Osm A-V toward the negative side or not, the blood flow in the femoral artery was decreased to one fifth (1/5) of the control flow without blood depletion. However, the decrease only in local blood flow failed to shift the Osm A-V toward the negative side or not, the blood flow in the femoral artery was decreased to one fifth (1/5) of the control flow without blood depletion. However, the decrease only in local blood flow failed to shift the Osm A-V toward the negative side (Table V). Furthermore, the negative shifting of the Osm A-V in the femoral artery and vein with blood depletion, as shown in Fig. 4, occurred simultaneously in both hindlimbs, and the fact that this shifting was obtained, as given in Table II, even when the local sympathetic nerve had been severed; it may indicate that this was a systemic reaction due to humoral factors and that it was derived from hemorrhagic hypotension.

The negative shifts of Osm A-V in the dog hindlimbs were also observed in acute venous congestion and that this finding was prevented by pretreatment with a sympathetic ganglion blocking agent. Imao as well as Baker observed that in acute venous congestion in the dog hindlimbs the diffusion capacity (that is PS; P: capillary permeability, S: the effective surface area of capillary vessels) in the congested area was reduced, and that this reaction disappeared by section of the sciatic nerve or a pretreatment with the sympathetic nerve blocking agent. The decrease of diffusion capacity was mostly based on the reduced effective surface area of capillary vessels and lead the peripheral tissue to hypoxic state. The author and his collaborators observed that the diffusion capacity in the dog hindlimbs decreased by 44% on the average in hemorrhagic hypotension, and postulated that because this reaction was retained even when the sympathetic nerve had been severed, it would have been derived from some humoral factor.

Fukuda observed experimentally in dogs an increase of serum catecholamines level with hemorrhagic hypotension. The increased blood catecholamines may contract the precapillary sphincter muscle to lead the tissues into a hypoxic state, and allow sodium and $\text{HCO}_3$ to be released into the plasma in the same mechanism as in acute venous congestion.

CONCLUSION

Mongrel dogs were anesthetized, and depleted of blood until a mean blood pressure of 60 mmHg was reached, and osmolality of peripheral arterial and venous blood were measured, and in a part of the experiments the effects of respiration and local blood flow on these osmolality were studied.

1) The osmolar arterio-venous difference shifted toward the negative side with hemorrhagic hypotension. The Na arterio-venous difference and $\text{HCO}_3$ arterio-venous difference shifted toward the negative side, but glucose arterio-venous difference and Cl arterio-venous difference toward the positive side. It was Na and $\text{HCO}_3$ that were mainly responsible for the negative shift of osmolar arterio-venous difference.

2) Though in controlled hyperventilation the osmolar arterio-venous difference shifted toward the negative side, in hemorrhagic hypotension under a constant controlled ventilation the osmolar arterio-venous difference shifted toward the negative side as well.

3) The negative shift of osmolar arterio-venous difference with hemorrhagic hypotension was reduced with an increase in local blood flow, but no negative shift of osmolar arterio-venous difference occured with a decrease in local blood flow without systemic blood depletion.

From these findings, it may be postulated that the negative Osm A-V that is observed in hemor-
Arterial and Venous Osmolalities Induced by Hemorrhagic Hypotension

Hemorrhagic hypotension is derived from the release of Na and HCO₃⁻ from the peripheral tissue; most probably from the skeletal muscle into the venous blood. The effects of volume of respiration and local blood flow on the peripheral osmolality were also discussed.

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