Hemodilution mediates hemodynamic changes during acute expansion in unanesthetized rats

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Hemodilution mediates hemodynamic changes during acute expansion in unanesthetized rats. Am J Physiol Regulatory Integrative Comp Physiol 279: R2243–R2251, 2000.—Studies were carried out to determine the relative importance of volume and hemodilution on hemodynamic adjustments to acute volume expansion. Systemic and renal hemodynamics were monitored in unanesthetized and unrestrained rats during progressive and equivalent blood volume expansion with saline (Sal; 1, 2, and 4% body wt), 7% BSA solution (0.35, 0.7, and 1.4% body wt), and reconstituted whole blood from donor rats (WBL; 0.35, 0.7, and 1.4% body wt). Mean arterial pressure remained unchanged in Sal and BSA but increased progressively in WBL-expanded rats (from 92 to 106 mmHg after maximal expansion). In Sal and BSA-expanded rats, cardiac output (CO) and renal blood flow (RBF) increased (CO: Sal from 19 to 20, 22, and 25; BSA from 21 to 23, 27, and 31; RBF: Sal from 1.6 to 1.8, 2.2, and 2.5; BSA from 2 to 24, 27, and 3.1 ml/min·100 g body wt⁻¹), whereas total peripheral (TPR) and renal vascular (RVR) resistance decreased in parallel with the expansions. After expansion with WBL, CO increased progressively but less extensively than in cell-free expanded rats (21 to 22, 24, and 26 ml/min·100 g body wt⁻¹), whereas TPR and RVR remained unchanged. Systemic hematocrit (Hct) decreased approximately the same after expansion with Sal or BSA solutions but remained unchanged after expansion with WBL. Isovolemic hemodilution to Hct levels comparable to those seen after maximal expansion with cell-free solutions also reduced SVR and RVR, although less extensively. These findings suggest that in unanesthetized rats hemodilution plays a major role in the systemic and renal hemodynamics during expansion.

The relative contribution of hemodilution to the effects of acute expansion in the systemic and regional hemodynamics is still controversial. Our work on this area started by studying the effects of hemodilution on renal hemodynamics during acute blood volume expansion in anesthetized rats (10, 11). It was demonstrated that renal vascular resistance decreases in parallel with the expansion level during graded expansion with cell-free solutions. No significant change in renal hemodynamics was observed during expansion with whole blood. Further experiments with pharmacological blockade of renal vascular tone and restoration of the hematocrit confirmed that hemodilution was the major factor responsible for the reductions in the renal vascular resistance during expansion with cell-free solutions. It was estimated that ~70% of this effect is related to the reduction in blood viscosity, whereas the remaining effect is related to active vasodilation. However, in these studies, some of the major regulators of renal vascular resistance such as renal perfusion pres-
ure and renal nerve activity were controlled or eliminated. This could exaggerate the dependence of renal vascular resistance on hematocrit. Moreover, the anesthesia could change the vascular reactivity and thus the relative contribution of dilation and reduction in blood viscosity to changes in vascular resistance during hemodilution. These difficulties could be overcome with studies under more physiological conditions. Moreover, studies including systemic hemodynamics could allow a better insight about the relative importance of hemodilution and volume on the hemodynamic adjustments during acute blood volume expansion.

Therefore, the protocols of the present study were designed to examine the relative importance of hemodilution and volume to the adjustments of systemic and renal hemodynamics during acute expansion in unanesthetized and unrestrained rats. Systemic and renal hemodynamics were monitored continuously during stepwise expansion with 0.9% saline, 7% BSA solutions, and whole blood. The effects of the expansions on systemic and renal hemodynamics were compared with the effects of isovolemic hemodilution.

METHODS

The experiments were performed on adult male Wistar rats (260–330 g) obtained from the University of Campinas’ Central Animal House. The rats were fed standard chow containing 1% NaCl.

Surgical Procedures

All surgical procedures were performed under aseptic conditions. Rats were anesthetized with a mixture of ketamine (70 mg/kg body wt im) and diazepam (6 mg/kg body wt im) and were placed on a temperature-controlled surgical table to maintain body temperature at 37°C. Rats used in experiments in which cardiac output was monitored were prepared as follows: the trachea was cannulated, and ventilation was controlled using a small rodent ventilator (Harvard Apparatus, South Natick, MA). The thoracic cavity was opened at the third right intercostal space, and the ascending aorta was dissected carefully, sparing the phrenic and the vagus nerves. An ultrasonic flow probe (2SB; Transonic Systems, Ithaca, NY) was then placed and adjusted to the ascending aorta after which the thoracic cavity was closed. Rats used in experiments in which renal blood flow was monitored were prepared as follows: the abdominal cavity was opened via a midline incision. The left kidney was identified, and the left renal artery was dissected free of the renal vein with care to avoid major damage in renal nerves. An ultrasonic flow probe (1RB; Transonic Systems) was then placed and adjusted to the renal artery in the retroperitoneal space between the superior pole of the left kidney and abdominal aorta. The 2SB and 1RB probe connectors were exteriorized at the back of the neck and sutured in a subcutaneous silicone port. Simultaneous to probe implantation, Tygon-tipped polyvinyl cannulas were placed in the lower abdominal aorta and inferior vena cava throughout the femoral artery and femoral vein, respectively. The cannulas were exteriorized at the back of the neck in a 25-cm length of stainless steel spring (0.5 cm in diameter). The spring was attached to a swivel (Instech) at the top of an individual cage that allowed the animal to move freely about its cage while being infused. At the end of the surgical procedures, the animals received single doses of antibiotic (Pentabiotic Veterinário, 100 mg/kg body wt). The animals were maintained in individual cages and allowed to recover for 5 days before the study.

Monitoring

Pulsatile arterial pressure, cardiac output, and renal blood flow were monitored continuously during the experimental period. The arterial catheter was connected to a COBE transducer (Arvada), and the signal was amplified with a GP4A Stemtech amplifier (Stemtech). The cable of the ultrasonic flow probe was connected to a T208 Transonic flowmeter. The amplifier and the flowmeter output were connected to an analog-to-digital board, and this was connected to a computer loaded with WINDAQ-PRO Data Acquisition software (DATAQ Instruments) for continuous monitoring and recording of hemodynamic parameters. Each signal was recorded in individual channels and was sampled at 100 Hz.

Preparation of Fluids and Donor Blood for Expansion

Saline (0.9%) and BSA (grade V; 3.5 and 7%; Sigma Chemical, St. Louis, MO) solutions were prepared fresh every day. Because blood withdrawal stimulates the release of a variety of vasoactive substances in the donor rat, the donor red blood cells were washed two times and resuspended in a Ringer solution containing 3.5% BSA as described before (10, 11).

Blood Chemical Analysis and Hematocrit Determination

Separate groups of rats were cannulated and expanded with saline (n = 4), 7% BSA (n = 4), and whole blood (n = 4) for hematocrit, arterial blood gases, pH, and plasma sodium and potassium measurements. Samples of arterial blood (200 μl) were collected in glass capillary tubes and were analyzed using a Chiron 348 Blood Gas System (Chiron Diagnostics, Halstead, UK).

Estimation of Systemic and Renal Vascular Resistance and Blood Viscosity

Total peripheral (TPR) and renal vascular (RVR) resistance was calculated from the pressure-flow ratios, as described by the equations TPR = MAP/CO and RVR = MAP/RBF, where MAP is mean arterial pressure, CO is cardiac output, and RBF is renal blood flow. The Vand equation (17) was used to estimate the apparent blood viscosity (η), as follows:

\[ \eta = \eta_{p}(1 + 0.025\text{Hct} + 7.35 \times 10^{-4}\text{Hct}^{2}) \]

where \( \eta_{p} \) is the plasma viscosity, considered as a fixed value of 1.2 cP (27), and Hct is the hematocrit.

Experimental Protocols

Protocol 1: Comparison of the effects of volume expansion with saline, BSA solutions, or whole blood on systemic and renal hemodynamics. Arterial pressure, cardiac output, and renal blood flow were measured for 30 min during the control period. The rats were then progressively expanded with saline (1, 2, and 4% of body wt; systemic hemodynamics n = 7, renal hemodynamics n = 5), BSA solution (0.35, 0.70, and 1.40% of body wt; systemic hemodynamics n = 5, renal hemodynamics n = 5), or whole blood (0.35, 0.70, and 1.40% of body wt; systemic hemodynamics n = 6; renal hemodynamics n = 5) in three steps of 25 min each while systemic and renal hemodynamics were monitored continuously. The volumes of various solutions were chosen to produce approximately the same degree of blood volume expansion. Because experimental evidence (8) indicates that only ~35% of a
saline infused volume remains in the intravascular compartment, the volumes of BSA solution and whole blood were adjusted to 35% of the value of saline infused.

Protocol 2: Isovolemic hemodilution. In these experiments, systemic \( (n = 5) \) and renal \( (n = 5) \) hemodynamics were monitored during a 30-min control period. At the end of this period, a syringe was connected to the femoral artery, and another syringe mounted in an infusion pump was connected to the cannula of femoral vein. A sample of blood (100 \( \mu l \)) was withdrawn for hematocrit and blood gas analysis. After blood collection, a blood volume corresponding to 1% of body weight was withdrawn from the femoral artery in a period of 10 min. During this period, an equivalent volume of a 3% BSA solution was infused continuously to restore the blood volume. Systemic and renal hemodynamics were monitored for 30 min more, and a new blood sample was collected for analysis.

Data and Statistical Analysis

The data are presented as means \( \pm \) SE. Differences between means were tested with one-way ANOVA for repeated measures and Bonferroni’s multiple range test. \( P < 0.05 \) was considered significant.

RESULTS

Comparison of Effects of Volume Expansion with 0.9% Saline, 7% BSA Solutions, and Whole Blood on Systemic and Renal Hemodynamics

The effects of graded expansion with saline on systemic hemodynamics are summarized in Fig. 1A. Cardiac output increased progressively from control values of 19 to 20, 22, and 25 ml\( \cdot \)min\(^{-1} \cdot 100\) g body wt\(^{-1}\) during expansion with volumes corresponding to 1, 2, and 4% of body weight (Fig. 1A). Stroke volume increased up to the expansion with a saline volume corresponding to 2% of body weight, remaining stable thereafter. Heart rate only increased significantly during the expansion with saline at a volume corresponding to 4% of body weight (Fig. 1B). Mean arterial pressure remained unchanged (\( \sim \)92 mmHg) during graded volume expansion, whereas total peripheral resistance decreased from 5 to 4.7, 4.2, and 3.9 mmHg\( \cdot \)ml\(^{-1} \cdot \)min\(^{-1} \cdot 100\) g body wt\(^{-1}\) (Fig. 1A).

Figure 2A summarizes the effect of expansion with saline on renal hemodynamics. As previously observed, arterial pressure remained unaltered during the graded volume expansion with saline. Renal blood flow augmented in parallel with the expansion up to 56% after expansion with a volume corresponding to 4% of body weight (from 1.6 to 1.8, 2.2, and 2.5 ml\( \cdot \)min\(^{-1} \cdot 100\) g body wt\(^{-1}\)). Renal vascular resistance decreased in parallel with expansion (from control values of 67 to 58, 48, and 44 mmHg\( \cdot \)ml\(^{-1} \cdot \)min\(^{-1} \cdot 100\) g body wt\(^{-1}\)).

The effects of volume expansion with 7% BSA solution were similar to those observed with saline (Fig. 3A). Cardiac output increased from 21 to 23, 27, and 31 ml\( \cdot \)min\(^{-1} \cdot 100\) g body wt\(^{-1}\). Stroke volume and heart rate changed as during graded volume expansion with

![Fig. 1. Systemic hemodynamics before (C) and after grading expansion with 0.9% saline solution (1, 2, and 4% of body wt). A: mean arterial pressure (MAP), cardiac output (CO), and total peripheral resistance (TPR). Hct, hematocrit; ru, resistance unit; bwt, body wt. B: heart rate (HR) and stroke volume (SV). *P < 0.05 compared with control values.](http://ajpregu.physiology.org/ by 10.220.33.4 on October 14, 2017)
saline (Fig. 3B). Mean arterial pressure remained stable (95 mmHg) while total peripheral resistance decreased from control levels of 4.5 to 4.3, 3.6, and 3.2 mmHg·ml⁻¹·min⁻¹·100 g body wt⁻¹ after infusions corresponding to 0.35, 0.7, and 1.4% of body weight, respectively.

Changes in renal hemodynamics during expansion with 7% BSA solution followed the same pattern observed during saline expansion (Fig. 2B). Renal blood flow increased by 56% (from basal 2 to 2.4, 2.7, and 3.1 ml·min⁻¹·100 g body wt⁻¹) and renal vascular resistance decreased by 38% (from 54 to 45, 40, and 34 mmHg·ml⁻¹·min⁻¹·100 g body wt⁻¹) after expansion with a volume corresponding to 1.4% of body weight.

Expansion with saline or 7% BSA solutions diluted the hematocrit in parallel with the level of volume expansion (Table 1). The changes were similar in both groups.

During infusion of whole blood, cardiac output rose in parallel with the expansion; however less extensively than during expansion with saline or BSA solution (Fig. 4A). Stroke volume increased progressively with the expansion level, whereas heart rate remained unchanged (Fig. 4B). In contrast to the expansion with saline and BSA solutions, expansion with whole blood increased arterial pressure in parallel with the expansion level. Arterial pressure increased from control levels of 92–106 mmHg after expansion with a volume corresponding to 1.4% of body weight. Total peripheral resistance did not change during expansion with whole blood.

No significant change was observed in renal blood flow or renal vascular resistance during expansion with whole blood (Fig. 2C). As expected, hematocrit did not change significantly after the expansion in this group of rats.

Plasma electrolytes, pH, arterial P O2, and arterial P CO2 (Paco2; Table 1) remained unchanged after expansion with the three different fluids, except for minor decreases in Paco2 and plasma potassium concentration during expansion with higher volumes of BSA solution. Expansion with both saline and BSA solutions reduced the oxygen content in arterial blood in parallel with the hemodilution (Table 2). However, the estimated oxygen transport remained unchanged due to the simultaneous increases in cardiac output.

**Effects of Isovolemic Hemodilution on Systemic Hemodynamics**

The results of these experiments are summarized in Fig. 5. The replacement of the animal's blood by a 3% BSA solution in a volume corresponding to 1% of body weight reduced the hematocrit from 47 to 36%. This maneuver did not change mean arterial pressure (~96 mmHg) but increased cardiac output by 20% (from 20

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**Fig. 2. Renal hemodynamics before (C) and after grading expansion. A: 0.9% saline solution (1, 2, and 4% of body wt). B: 7% BSA solution (0.35, 0.7 and 1.4% of body wt). C: whole blood (0.35, 0.7, and 1.4% of body wt). RBF, renal blood flow; RVR, renal vascular resistance. *P < 0.05 compared with control values; n, no. of rats.**
to 24 ml·min⁻¹·100 g body wt⁻¹) and decreased total peripheral resistance by 18% (from 4.9 to 4 mmHg·ml⁻¹·min⁻¹·100 g body wt⁻¹). Heart rate increased while stroke volume remained unaltered. The arterial blood oxygen content decreased by 32%, but the estimated arterial blood oxygen transport remained essentially constant (Table 2). After the isovolemic hemodilution, blood gas and plasma electrolyte concentration remained unchanged. The results of the experiments in which renal hemodynamics were monitored are summarized in Fig. 6. In this group, isovolemic hemodilution reduced the hematocrit from 43 to 31% and was accompanied by a 20% increase of renal blood flow (from 1.5 to 1.8 ml·min⁻¹·100 g body wt⁻¹) and a decrease of 22% in renal vascular resistance (from 76 to 59 mmHg·ml⁻¹·min⁻¹·100 g body wt⁻¹), whereas mean arterial pressure remained unchanged.

Estimation of Changes in Blood Viscosity Induced by Volume Expansion

Table 3 shows the estimated blood viscosity of all groups obtained with the Vand equation. As expected, calculated blood viscosity declined progressively with the decrease in the hematocrit in rats expanded with saline or 7% BSA solutions and in rats that underwent isovolemic hemodilution. Calculated blood viscosity decreased by ~20% (from 4 to 3.2 cP) after maximal expansion with 0.9% saline. After maximal expansion with 7% BSA solution, the estimated blood viscosity decreased by ~35%. No significant change in hematocrit and in blood viscosity was observed after expansion.
with whole blood. Isovolemic hemodilution reduced the estimated blood viscosity by ~26%.

**DISCUSSION**

In this study, the changes in systemic and renal hemodynamics occurring during equivalent blood volume expansion with cell-free solutions and whole blood were recorded comprehensively and compared in unanesthetized rats. The results are compatible with the notion that the changes in total peripheral and renal vascular resistance during expansion with cell-free solutions are mainly related to hemodilution. This is suggested by the marked differences observed in the effects of expansion with cell-free solutions and whole blood in systemic and renal hemodynamics. Graded volume expansion with saline or a 7% BSA solution was accompanied by increases in cardiac output and renal blood flow, along with reductions in total peripheral and renal vascular resistance without detectable changes in mean arterial pressure. Remarkably, similar reductions were seen for total peripheral and renal vascular resistance. Otherwise, expansion with whole blood increased mean arterial pressure in parallel with cardiac output without significant changes in vascular resistance. Saline and 7% BSA solutions reduced hematocrit to the same level; there were no changes when whole blood was used. Additional experiments were performed to confirm that hemodilution alone could reduce systemic and renal vascular resistance in unrestrained rats. In these experiments, hematocrit was reduced by isovolemic hemodilution to levels comparable to those seen after maximal expansion with cell-free solutions. This reduced total and renal vascular resistance to ~65% of that observed after expansion with cell-free solutions. Overall, these results confirmed, in unanesthetized and unrestrained rats, our previous observation that hemodilution, rather than hormonal or neural mechanisms triggered by volume expansion, plays a major role in the reductions of renal vascular resistance during expansion with cell-free solutions and extended this observation to the systemic circulation.

Our data bring into discussion the relative contribution of rheologic vs. vascular factors to the adjustments of total and renal vascular resistance occurring during acute blood volume expansion. On a broad base, flow resistance consists of a structural component, which depends on the vessels’ length and diameter, and blood viscosity, which varies mainly as a function of the hematocrit (26). Hemodilution changes the physical properties of blood by reducing the number of circulating red blood cells, thus decreasing its viscosity and the

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**Fig. 4.** Systemic hemodynamics before (C) and after grading expansion with whole blood (0.35, 0.7, and 1.4% of body wt). A: MAP, CO, and TPR. B: HR and SV. *P < 0.05 compared with control values.
oxygen-carrying capacity. Both mechanisms could mediate the reduction of total and renal vascular resistance during acute blood volume expansion with cell-free solutions. However, reductions of the systemic hematocrit down to 20–25% have been shown to decrease vascular resistance mainly due to the decrease in blood viscosity (18, 25). Accordingly, in the present study, volume expansion with cell-free solutions and isovolemic hemodilution reduced the hematocrit to a minimum of ~33%, suggesting that most of the hemo-

### Table 2. Blood gas

<table>
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<tr>
<th>Protocol</th>
<th>pH</th>
<th>$P_{\text{CO}_2}$</th>
<th>$C_{\text{CO}_2}$</th>
<th>$P_{\text{O}_2}$</th>
<th>$O_2$</th>
<th>Hct</th>
<th>Hbct</th>
<th>$O_2$ Transport</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>C</td>
<td>7.5 ± 0.01</td>
<td>30 ± 3.62</td>
<td>26 ± 2.30</td>
<td>107 ± 12.2</td>
<td>98 ± 0.31</td>
<td>20 ± 0.62</td>
<td>42 ± 1.19</td>
</tr>
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<td></td>
<td>1%</td>
<td>7.5 ± 0.01</td>
<td>32 ± 1.03</td>
<td>25 ± 1.07</td>
<td>106 ± 14.2</td>
<td>98 ± 0.42</td>
<td>17 ± 1.32</td>
<td>37 ± 2.72</td>
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<td>2%</td>
<td>7.5 ± 0.02</td>
<td>32 ± 2.28</td>
<td>24 ± 1.97</td>
<td>99 ± 9.54</td>
<td>98 ± 0.36</td>
<td>17 ± 11.25</td>
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<td></td>
<td>4%</td>
<td>7.5 ± 0.02</td>
<td>33 ± 2.11</td>
<td>25 ± 1.77</td>
<td>94 ± 9.06</td>
<td>97 ± 0.68</td>
<td>16 ± 1.09</td>
<td>33 ± 2.10</td>
</tr>
<tr>
<td>BSA 7%</td>
<td>C</td>
<td>7.5 ± 0.01</td>
<td>39 ± 2.07</td>
<td>29 ± 1.61</td>
<td>83 ± 4.91</td>
<td>97 ± 0.51</td>
<td>21 ± 0.37</td>
<td>45 ± 0.33</td>
</tr>
<tr>
<td></td>
<td>0.35%</td>
<td>7.5 ± 0.01</td>
<td>35 ± 1.33</td>
<td>28 ± 0.92</td>
<td>83 ± 2.78</td>
<td>97 ± 0.23</td>
<td>17 ± 0.84</td>
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<td>0.7%</td>
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<td>32 ± 1.42</td>
<td>26 ± 0.05</td>
<td>83 ± 1.44</td>
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<td>16 ± 1.01</td>
<td>34 ± 3.28</td>
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<td></td>
<td>1.4%</td>
<td>7.5 ± 0.01</td>
<td>32 ± 1.73</td>
<td>25 ± 0.99</td>
<td>86 ± 2.02</td>
<td>97 ± 0.21</td>
<td>15 ± 1.06</td>
<td>31 ± 2.91</td>
</tr>
<tr>
<td>Whole blood</td>
<td>C</td>
<td>7.5 ± 0.02</td>
<td>39 ± 1.74</td>
<td>31 ± 1.26</td>
<td>88 ± 5.42</td>
<td>97 ± 0.50</td>
<td>21 ± 0.57</td>
<td>45 ± 1.32</td>
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<tr>
<td></td>
<td>0.35%</td>
<td>7.5 ± 0.01</td>
<td>37 ± 0.97</td>
<td>31 ± 1.00</td>
<td>84 ± 3.24</td>
<td>97 ± 0.46</td>
<td>20 ± 0.64</td>
<td>43 ± 0.96</td>
</tr>
<tr>
<td></td>
<td>0.7%</td>
<td>7.5 ± 0.01</td>
<td>35 ± 1.16</td>
<td>30 ± 0.47</td>
<td>87 ± 2.24</td>
<td>97 ± 0.19</td>
<td>20 ± 0.76</td>
<td>44 ± 1.68</td>
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<tr>
<td></td>
<td>1.4%</td>
<td>7.5 ± 0.01</td>
<td>37 ± 1.61</td>
<td>30 ± 1.03</td>
<td>86 ± 1.12</td>
<td>97 ± 0.12</td>
<td>23 ± 1.36</td>
<td>49 ± 2.98</td>
</tr>
<tr>
<td>Isovolemic hemodilution (systemic)</td>
<td>C</td>
<td>7.5 ± 0.01</td>
<td>40 ± 1.79</td>
<td>31 ± 1.20</td>
<td>84 ± 5.81</td>
<td>97 ± 0.42</td>
<td>22 ± 0.73</td>
<td>47 ± 1.73</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>7.5 ± 0.02</td>
<td>37 ± 1.26</td>
<td>28 ± 0.54</td>
<td>77 ± 4.85</td>
<td>96 ± 0.50</td>
<td>15 ± 1.83</td>
<td>36 ± 2.31</td>
</tr>
<tr>
<td>Isovolemic hemodilution (renal)</td>
<td>C</td>
<td>7.5 ± 0.01</td>
<td>43 ± 1.88</td>
<td>32 ± 0.78</td>
<td>85 ± 2.88</td>
<td>97 ± 0.37</td>
<td>20 ± 0.8</td>
<td>43 ± 2</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>7.5 ± 0.01</td>
<td>32 ± 0.9</td>
<td>27 ± 0.62</td>
<td>81 ± 2.46</td>
<td>97 ± 0.23</td>
<td>15 ± 0.4</td>
<td>31 ± 1</td>
</tr>
</tbody>
</table>

Values are means ± SE. $P_{\text{CO}_2}$, arterial pressure of carbon dioxide (mmHg); $C_{\text{CO}_2}$, arterial carbon dioxide content; $P_{\text{O}_2}$, arterial pressure of oxygen (mmHg); $O_2$, oxygen saturation (%); $O_2$, $O_2$ content; Hct, hematocrit (%); Hbct, hemoglobin content (%). *$P < 0.05$ compared with control values.

**Fig. 5.** Systemic hemodynamics before (C) and after isovolemic hemodilution with 3% BSA solution (H). A: MAP, CO, and TPR. B: HR and SV. *$P < 0.05$ compared with control values.
Dynamic effects were related to the reduction in blood viscosity. This was seen quantitatively by the reduction in blood viscosity estimated by the Vand equation that was proportional to the decrease of total and renal vascular resistance. On the other hand, we estimated that the oxygen transport to the tissues was maintained constant after expansion with cell-free solutions or isovolemic hemodilution, indicating that the tissue oxygenation was unaffected by the levels of hematocrit reductions seen in the present study. This further supports the hypothesis that the effects of hemodilution on systemic and renal hemodynamics are mediated by the reduction in viscosity rather than by the reduction in tissues oxygen levels.

Comparisons of the falls in total and renal vascular resistance of rats that underwent expansion with cell-free solutions and isovolemic hemodilution may give additional insight into the matter of the relative importance of vasodilation and blood viscosity to the reduction of vascular resistance during acute expansion. Although total and renal vascular resistance decreased during both conditions, these decreases were less expressive after isovolemic hemodilution, even though the hematocrit fell to the same extent. The reductions in total and renal vascular resistance after isovolemic hemodilution were only ~65% of those observed after hemodilution with expansion. The additional decrease in total and renal vascular resistance seen during expansion with cell-free solutions could be explained by vasodilation. Similar values were observed in our previous studies (10, 11) on the relative contribution of hemodilution and vasodilation to renal vascular resistance during acute expansion in anesthetized rats.

This accompanying vasodilation during volume expansion with cell-free solutions could be attributed to various mechanisms. Results from our previous studies (10, 11) suggested that hemodilution, by reducing blood viscosity, may influence vascular tone. By increasing the flow and shear rates, hemodilution increases wall shear stress, which would be the stimulus to dilate blood vessels. However, this hypothesis needs further experimental support to be confirmed. This vasodilation also could be due to volume-dependent activation or suppression of neural or hormonal mechanisms involved in cardiovascular control. Indeed, such mechanisms have been thought to play a central role on cardiovascular responses to acute blood volume expansion (2). Accordingly, it has been shown (1) that cardiopulmonary mechanoceptors are activated by volume expansion and result in a reduction of sympathetic nerve activity, mainly in the kidney. However, the contribution of this reduction to the hemodynamic adjustments during expansion remains unclear. Although sympathetic tone inhibition is important for natriuresis that occurs during expansion, it is probably of less importance for hemodynamic changes observed in the renal circulation (5). However, sympathetic tone inhibition may be important in territories with high basal tone such as skeletal muscles, for example (1). The absence of significant changes in total and renal vascular resistance during equivalent expansion with whole blood seen in the present study is in accordance with the hypothesis that reflex mechanisms triggered by increases in central volume are not the dominant mechanism for the hemodynamic adjustments during acute expansion in unanesthetized rats. Accordingly, it has been shown previously (7) that expansion with plasma-like fluids reduces systemic vascular resistance whether or not the cardiovascular reflex control mechanisms were intact. Moreover, the decrease in the peripheral resistance observed after expansion with

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**Table 3. Blood viscosity**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>η</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>4.0 ± 0.13</td>
</tr>
<tr>
<td>1%</td>
<td>3.5 ± 0.25</td>
</tr>
<tr>
<td>2%</td>
<td>3.4 ± 0.23*</td>
</tr>
<tr>
<td>4%</td>
<td>3.2 ± 0.19*</td>
</tr>
<tr>
<td>BSA 7%</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>4.4 ± 0.04</td>
</tr>
<tr>
<td>0.35%</td>
<td>3.6 ± 0.18*</td>
</tr>
<tr>
<td>0.7%</td>
<td>3.3 ± 0.19*</td>
</tr>
<tr>
<td>1.4%</td>
<td>3.0 ± 0.25*</td>
</tr>
<tr>
<td>Isovolemic hemodilution</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>4.4 ± 0.15</td>
</tr>
<tr>
<td>H</td>
<td>3.1 ± 0.14</td>
</tr>
</tbody>
</table>

Values are means ± SE. η, Blood viscosity during expansion with 0.9% saline, 7% BSA, and isovolemic hemodilution protocol; H, after hemodilution. *P < 0.05 compared with control values.
cell-free solutions was independent of changes in blood volume, atrial pressure, blood pressure, or arterial blood oxygen tension. The only consistent association was with the degree of hemodilution, suggesting again that changes in the hematocrit, and presumably in blood viscosity, could be the mechanism underlying this response.

Acute volume expansion increases circulating levels of atrial natriuretic peptide (ANP), which potentially might cause systemic and renal vasodilation. A rise in the circulating levels of ANP has been suggested to be the major determinant of the reduction of renal vascular resistance during expansion (4, 19). However, a contribution of this mechanism to hemodynamic changes after expansion with cell-free solutions is inconsistent with the fact that infusion of whole blood, despite producing comparable volume expansion, was not accompanied by a significant decrease in systemic or renal vascular resistance.

Finally, changes in arterial pressure during expansion might bring additional complexities to the responses. The absence of consistent changes in arterial pressure during acute expansion might help to explain the dominance of the effects associated with hemodilution over the neural reflex mechanism in the hemodynamic regulation after expansion with cell-free solutions.

In conclusion, the results of the present study indicate that, in unanesthetized and unrestrained rats, the fall in hematocrit rather than volume and its effect on vascular tone through modulation of neurohormonal mechanisms is the most important factor mediating changes in total and renal vascular resistance during acute volume expansion with cell-free solutions. This important role of hemodilution on changes in vascular resistance is probably related to the fall in viscosity of the blood.

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