Circulatory Pressure-Volume Relationship and Cardiac Output in DOCA-Salt Rats

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SUMMARY We studied the total vascular pressure-volume relationship and cardiac output (CO) in conscious rats receiving DOCA-salt or sham treatment. The mean circulatory filling pressure (MCFP) was measured by briefly inflating an indwelling balloon in the right atrium, and the MCFP-blood volume (BV) relationship over ± 10% of BV was determined by rapid blood infusion or withdrawal. CO was measured in separate experiments using Fick’s principle. Arterial pressure-volume relationship was also determined in additional experiments on anesthetized rats. Compared with sham rats, the mean arterial pressure was unchanged at 1 week, increased at 2 weeks, and increased further thereafter in the DOCA-salt rats. The BV was unchanged at 1 week, expanded at 2 weeks, unchanged at 5 weeks, and contracted at 8 weeks. There were no significant changes in MCFP, total vascular compliance (the inverse of the slope), nor unstressed volume (extrapolated volume axis intercept) at 2, 5, and 8 weeks. Total vascular capacity, assessed as BV at MCFP of 7.6 mm Hg, increased at 2 weeks, was unchanged at 5 weeks, and decreased at 8 weeks. Arterial compliance decreased at 5 and 8 weeks. CO remained unaltered at 1, 2, 5, and 8 weeks. These results suggest that the altered total vascular capacity may serve to maintain a normal CO against a rising afterload in the conscious DOCA-salt hypertensive rats, and that the decreased total vascular capacity may be a secondary hemodynamic feature with progression of hypertension. (Hypertension 5: 507-513, 1983)

KEY WORDS • mean circulatory filling pressure • blood volume • total vascular compliance • arterial compliance • unstressed volume

CIRCULATING blood volume (BV) and circulatory capacity are essential determinants of cardiac filling pressure and hence cardiac output (CO), and therefore play an integral role in arterial pressure regulation. There is growing evidence that venous capacity or compliance is decreased in many forms of experimental and clinical hypertension. One approach to the study of venous filling function is the determination of mean circulatory filling pressure (MCFP), an index of total vascular, quantitatively venous, capacity for any given BV. Increased MCFP associated with normal or decreased BV, which reflects decreased total vascular capacity, has been observed in several forms of experimental hypertension resulting from one-kidney Page’s procedure, one- and two-kidney Goldblatt’s procedure, angiotensin II infusion and genetic origin. However, to our knowledge, whole-body vascular capacity has not been investigated in DOCA-salt hypertension, a most extensively studied model of mineralocorticoid hypertension. The main purpose of the present study was to determine the total vascular pressure-volume relationship in this form of rat hypertension, utilizing a MCFP-BV approach. In view of the important participation of venous capacity in CO control and the paucity of CO data in a rat model, we also determined CO in a separate experiment, using the Fick method.

Methods

Male Wistar rats weighing between 210 and 270 g were anesthetized with ether, and a left nephrectomy was carried out. Seven days after surgery, the rats were randomly divided into two groups. One group was given weekly subcutaneous (s.c.) injections of deoxycorticosterone acetate (30 mg/kg) in sesame oil and
allowed to drink 1% saline ad libitum (DOCA-salt group). The other group was injected with equivalent volumes of sesame oil and given tap water to drink (sham group). Both had free access to a standard laboratory chow.

Experiments were carried out at 1, 2, 5, and 8 weeks following the initiation of DOCA-salt or sham treatment. Rats (n = 180) were subjected to one of three sets of experiments at 2, 5 and 8 weeks, and exclusively to Experiment 1 at 1 week. A pair of rats from either the DOCA-salt or sham group, which had been treated for an identical period, were used for the same set of experiments on the same day. Only healthy rats were used.

On the day of the experiments and 1 week after the injections, each rat was anesthetized with ether and a vessel cannulation performed, as described below. The wounds were treated with 1% lidocaine during surgery, and the incisions were closed. All catheters were led out at the back of the neck. Three hours were allowed for the rats to recover from surgery and anesthesia before the start of experiments.

**Experiment 1**

CO was determined in conscious rats by the direct Fick method. The right ventricle via the right jugular vein, and the left femoral artery and vein were cannulated with PE-50 tubing. After recovering, each rat was placed in a small plexiglass chamber that was immersed in a water bath and connected in series to a 1 liter spirometer (Warren Collins, Braintree, Massachusetts), a blower for air recirculation, a flask of soda lime, and a bubbling flask of saturated sodium hydroxide solution for carbon dioxide absorption, thus constituting the air-tight closed system. The cannulas were brought out of the chamber via a rubber stopper. Arterial pressure was recorded by a Statham transducer and brought out of the chamber via a rubber stopper. Arterial to venous compliance ratio in the rat. We used plasma samples determined by a hemolysis-oxygen technique, using a polarographic sensor (Yellow Springs Instruments, Yellow Springs, Ohio). CO was calculated as: CO = O2 consumption x 100/arteriovenous O2 content (vol%). Total peripheral resistance (TPR) was calculated as the quotient of MAP divided by CO.

**Experiment 2**

MCFP and MCFP-BV curves were measured by a method reported previously by Yamamoto et al. We placed appropriate catheters in the thoracic inferior vena cava via the left femoral vein, in the left femoral artery and in the right carotid artery, and a balloon-tipped catheter in the right atrium via the right jugular vein. After recovery, each rat was placed in a small unconfining box. The femoral artery and inferior vena cava pressures were recorded. A baseline pressure was set at cardiac level. Central venous pressure (CVP) was calibrated with a water manometer. After a 30-minute period of stabilization, PV was measured and BV calculated as described in Experiment 1. MCFP was measured by inflating the balloon in the right atrium and reading arterial and central venous pressures. With balloon distention, which arrests the circulation, CVP increased and reached a plateau within 4 to 5 seconds, while arterial pressure simultaneously decreased. The balloon was quickly deflated, and the circulation was immediately restored. Both pressures seldom reached the equilibrium, suggesting that some blood remained trapped in the arterial tree. To correct this, MCFP was obtained as MCFP = VPP + K(LAP - VPP), where VPP is venous plateau pressure, LAP is lowest arterial pressure, and K is the arterial to venous compliance ratio in the rat. We used 1/60 as the value of K, as in earlier studies, although slightly different values were reported in spontaneously hypertensive rats (SHR) and Wistar Kyoto rats (WKY) (see Results). It has been shown that with this method MCFP can be measured without causing significant hemodynamic and volume effects and reflex vasoconstriction.

To determine MCFP-BV relationships, MCFP was also measured immediately after changing BV (approximately 10% of total BV, i.e., ± 6.0 ml/kg) by rapidly infusing fresh donor (group-matched) rat blood into, or withdrawing blood from, the carotid artery. MCFP measurements were started 4 seconds after the initiation of the BV change and were completed within 4 to 5 seconds. The BV was immediately restored to the preexisting level. A final control MCFP was measured following the BV perturbation procedure. The average of two control measurements represented the baseline MCFP. A MCFP-BV relationship was calculated in each rat from these four data-points by regression analysis using the method of least squares. The reciprocal of the slope and the extrapolated volume axis intercept of this line were taken as estimates of total vascular compliance and unstressed intravascular volume (V’o), respectively. In addition, BV at MCFP of 7.6 mm Hg was taken as a quantitative estimate of total vascular capacity (Cav), where MCFP of 7.6 mm Hg was the average of values in all groups of rats, thus being close to the midpoints of the MCFP-BV curves (see Results).

**Experiment 3**

Systemic arterial pressure-volume relationship was determined according to the method of Samar and...
Coleman. Rats were prepared exactly as in Experiment 1. Three hours after cannulation, the rats were anesthetized with sodium pentobarbital (45 mg/kg, i.p.), and were placed on a heating pad, by which rectal temperature could be maintained at 37°C. Blood flow was briefly arrested by inflating the right atrial balloon, and at this point, the systemic arterial compartment and its volume were isolated. During this brief flow arrest, a small amount of blood was rapidly infused into or removed from the arterial compartment through the carotid arterial catheter, and subsequent pressure changes were measured through the femoral arterial catheter. Volume infusion or withdrawal (± 0.03 to ± 0.3 ml) was completed within 1 second. Approximately 10 data-points were obtained for each rat, and pressure-volume curves were thus constructed. Over the linear portion of the curve, the slope was calculated by the use of the least square regression analysis. The inverse of the slope represents an estimate of systemic arterial compliance.

Statistical Analysis

All results are presented as the means ± se. Comparisons were made between the DOCA-salt- and control sham-treated rats using Student's t test. Probability level of less than 0.05 was considered to be statistically significant.

Results

Since body weight, MAP, and fluid volumes in Experiments 1 and 2, conducted on conscious unrestrained animals, were virtually identical, all data were pooled and are shown in figure 1. As compared with control sham rats, body weight was similar at 1, 2, and 5 weeks after initiation of treatment, whereas it was significantly decreased at 8 weeks (350 ± 5 g vs 385 ± 6 g, p < 0.01). In the DOCA-salt rats, MAP was unchanged at 1 week (117 ± 3 mm Hg vs 111 ± 3 mm Hg, NS), was mildly but significantly elevated at 2 weeks (137 ± 3 mm Hg vs 117 ± 2 mm Hg, p < 0.01), was further elevated at 5 weeks (155 ± 3 mm Hg vs 117 ± 2 mm Hg, p < 0.01), and reached an extreme height at 8 weeks (192 ± 6 vs 115 ± 3 mm Hg, p < 0.01). The DOCA-salt rats showed unchanged PV, BV, and hematocrit (Hct) at 1 week; slightly but significantly expanded PV (41.8 ± 0.8 ml/kg vs 38.3 ± 0.9 ml/kg, p < 0.01) and BV (64.9 ± 1.0 ml/kg vs 60.7 ± 1.4 ml/kg, p < 0.05) and significantly reduced Hct (44.4 ± 0.6 vol% vs 46.6 ± 0.6 vol%, p < 0.05) at 2 weeks; and unchanged PV (40.0 ± 1.2 ml/kg vs 37.5 ± 1.0 ml/kg, NS), BV (62.1 ± 1.4 ml/kg vs 59.5 ± 1.3 ml/kg, NS), and Hct (44.8 ± 0.8 vol% vs 46.3 ± 0.8 vol%, NS) at 5 weeks. In contrast, there were significantly contracted PV (34.1 ± 1.1 ml/kg vs 38.0 ± 0.9 ml/kg, p < 0.01) and BV (56.6 ± 1.0 ml/kg vs 60.2 ± 1.1 ml/kg, p < 0.05), and significantly increased Hct (50.4 ± 1.1 vol% vs 45.8 ± 0.9 vol%, p < 0.01) at 8 weeks. No significant differences existed in HR at any time period studied.

The total vascular pressure-volume data are shown in figure 2 and table 1. The MCFP-BV curves were...
TABLE 1. Total Vascular Pressure-Volume Data in Conscious DOCA-Salt and Sham Rats

<table>
<thead>
<tr>
<th>No. of rats</th>
<th>2 weeks</th>
<th>5 weeks</th>
<th>8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DOCA-salt</td>
<td>Sham</td>
<td>DOCA-salt</td>
</tr>
<tr>
<td>MCFP (mm Hg)</td>
<td>7.4 ± 0.2</td>
<td>7.3 ± 0.2</td>
<td>8.2 ± 0.3</td>
</tr>
<tr>
<td>Compliance (ml/kg/mm Hg⁻¹)</td>
<td>3.28 ± 0.12</td>
<td>3.14 ± 0.13</td>
<td>2.95 ± 0.14</td>
</tr>
<tr>
<td>CaTV (ml/kg)</td>
<td>65.0* ± 1.3</td>
<td>64.0 ± 1.3</td>
<td>60.7 ± 1.2</td>
</tr>
<tr>
<td>V'o (ml/kg)</td>
<td>40.1 ± 1.6</td>
<td>36.9 ± 1.5</td>
<td>38.1 ± 1.5</td>
</tr>
</tbody>
</table>

Values are means ± SE. MCFP = mean circulatory filling pressure; Compliance = total vascular compliance; CaTV = total vascular capacity or blood volume at MCFP of 7.6 mm Hg; V'o = volume-axis intercept of MCFP-BV curve. *p < 0.05 in comparison with sham rats.

virtually linear. MCFP did not differ significantly between either group at any time period, although it tended to increase in the 5- and 8-week DOCA-salt rats. Neither total vascular compliance nor V'o exhibited significant differences between both groups at any time period. In the DOCA-salt groups, CaTV was significantly increased at 2 weeks, unaltered at 5 weeks, and significantly decreased at 8 weeks (table 1).

Systemic arterial compliance was not significantly different between the DOCA-salt and sham group at 2 weeks, but was significantly reduced in the DOCA-salt groups at 5 and 8 weeks (table 2). Because of these significant differences, we attempted to estimate the ratio of arterial to venous compliances in our DOCA-salt and sham rats. Herein, total vascular compliance was taken as total venous compliance. When comparing systemic arterial compliance to total venous compliance, we found this ratio to be about 1/80 in all control sham rats and the 2-week DOCA-salt rats, about 1/100 in the 5-week DOCA-salt groups, and about 1/110 in the 8-week DOCA-salt rats. Using this new ratio in each group of animals, we recalculated MCFP and MCFP-BV relationships. However, there were virtually no differences in any of the data (not shown), thus confirming the notion that the exact value for this ratio is not so critical in calculating MCFP.

As shown in table 3, no significant differences were detected in total O₂ consumption, arterial and venous blood O₂ contents, and arteriovenous blood O₂ content differences between the groups at any time period. There were also no significant differences in CO₂, whether expressed as an absolute value or as per body weight. In the DOCA-salt groups, total peripheral resistance was not significantly altered at 1 week, while it was significantly increased at 2 weeks (1.32 ± 0.08 mm Hg/ml/min vs 1.12 ± 0.04 mm Hg/ml/min, p < 0.05); at 5 weeks (1.39 ± 0.05 mm Hg/ml/min vs 1.12 ± 0.06 mm Hg/ml/min, p < 0.01); and at 8 weeks (2.23 ± 0.19 mm Hg/ml/min vs 1.01 ± 0.05 mm Hg/ml/min, p < 0.01).

Discussion

In using the MCFP-BV approach for quantitative assessment of whole-body vascular capacity, it is necessary to give attention to possible influences from reflex changes in venous tone, transcapillary fluid shift and stress relaxation/reverse stress relaxation that might be evoked by the volume perturbation procedure. These factors might rotate the MCFP-BV curve around the baseline data-point, thereby distorting the slope and the extrapolated volume axis intercept. To minimize these potential influences in the present study, smaller BV changes were made more rapidly and less frequently; the measurement of MCFP was completed 9 to 10 seconds after the start of ± 10% BV changes in the present study, whereas it was completed 10 to 14 seconds after that of ±7.5% and ±15% BV changes in the previous ones. The average changes of MCFP were ± 2.0 mm Hg. The resultant fluid shift and stress relaxation/reverse stress relaxation within this time frame and pressure alterations

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Table 3. Oxygen Consumption and Cardiac Output in Conscious DOCA-Salt and Sham Rats

<table>
<thead>
<tr>
<th></th>
<th>DOCA-salt</th>
<th>DOCA-salt</th>
<th>DOCA-salt</th>
<th>DOCA-salt</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of rats</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>O₂ consumption</td>
<td>26.8</td>
<td>26.2</td>
<td>27.1</td>
<td>26.7</td>
</tr>
<tr>
<td>ml/min/kg</td>
<td>±0.9</td>
<td>±1.1</td>
<td>±0.8</td>
<td>±0.7</td>
</tr>
<tr>
<td>Arterial O₂ content</td>
<td>19.1</td>
<td>18.9</td>
<td>19.1</td>
<td>18.7</td>
</tr>
<tr>
<td>vol%</td>
<td>±0.5</td>
<td>±0.6</td>
<td>±0.4</td>
<td>±0.5</td>
</tr>
<tr>
<td>Venous O₂ content</td>
<td>11.1</td>
<td>10.4</td>
<td>11.1</td>
<td>10.4</td>
</tr>
<tr>
<td>vol%</td>
<td>±0.5</td>
<td>±0.5</td>
<td>±0.5</td>
<td>±0.4</td>
</tr>
<tr>
<td>AV O₂ difference</td>
<td>8.0</td>
<td>8.5</td>
<td>8.0</td>
<td>8.4</td>
</tr>
<tr>
<td>vol%</td>
<td>±0.5</td>
<td>±0.5</td>
<td>±0.5</td>
<td>±0.4</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>95</td>
<td>89</td>
<td>106</td>
<td>98</td>
</tr>
<tr>
<td>ml/min</td>
<td>±6</td>
<td>±6</td>
<td>±7</td>
<td>±6</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>352</td>
<td>309</td>
<td>346</td>
<td>323</td>
</tr>
<tr>
<td>ml/min/kg</td>
<td>±15</td>
<td>±11.1</td>
<td>±20</td>
<td>±17</td>
</tr>
<tr>
<td>TPR</td>
<td>1.25</td>
<td>1.27</td>
<td>1.32*</td>
<td>1.12</td>
</tr>
<tr>
<td>mm Hg/ml/min</td>
<td>±0.06</td>
<td>±0.05</td>
<td>±0.08</td>
<td>±0.04</td>
</tr>
</tbody>
</table>

Values are means ± se. AV O₂ difference = arteriovenous O₂ difference; TPR = total peripheral resistance.

* p < 0.05, † p < 0.01, in comparison with sham rats.

would have minimal effects. Yet, reflex influences cannot be completely excluded in animals with intact autonomic reflexes. Trippodo et al. found total vascular compliance to be 3.1 ml/kg-mm Hg⁻¹ in thoracic-spinal cord-transected (autonomic-reflex-eliminated) rats in which approximately normal vascular capacity was maintained by epinephrine infusion, while we found this value to be 3.1–3.2 ml/kg-mm Hg⁻¹ in our control groups of rats (table 1). The similarity of both values would imply the relatively insignificant involvement of reflex influences under the conditions of the present experiments. Furthermore, it is reasonable to assume that the value of \( C_{av} \) would have negligible influences from those factors because of its location close to the midpoint of the MCFP-BV curve.

Our study is the first evaluation of total vascular pressure-volume relationship and cardiac output in DOCA-salt hypertensive rats. The PV and BV were slightly, but significantly, expanded at 2 weeks after initiating the DOCA-salt regimen, then reverted toward normal at 5 weeks, and were significantly contracted at 8 weeks (fig. 1). Despite these alterations, MCFP remained unchanged, although it tended to increase at 5 and 8 weeks. Based on these relative changes in BV and MCFP, total vascular capacity was deemed to be increased at 2 weeks, unchanged at 5 weeks, and decreased at 8 weeks. This was further demonstrated quantitatively by obtaining corresponding changes in \( "C_{av}\) at each time period (table 1). However, neither total vascular compliance nor \( V'0 \) was significantly altered, implying that subtle alterations in both may have contributed to the observed differences. The relative contributions of compliance or \( V'0 \) changes were sometimes difficult to ascertain because of technical difficulties dealing with the inherently nonlinear elasticity of the vascular system in an intact, whole-body preparation, as described above and elsewhere. " V. Figure 2 not only shows the linear MCFP-BV relationship over the data-points measured, but also suggests that a substantial extrapolation is required to arrive at \( V'0 \).

Therefore, it is not surprising to come across controversial results in the literature. At least two reports are available on the MCFP-BV curves in SHR and its normotensive counterpart, WKY. Samar and Coleman observed increased MCFP with unaltered BV, unaltered compliance, and marginally decreased \( V'0 \) in conscious SHR, whereas Haraldsson et al. investigated anesthetized SHR in which the vasculature was made to relax and was free from sympathetic tone by a combination of hexamethonium and papaverine, found decreased venous capacity, decreased compliance, and unaltered \( V'0 \). In studies on the MCFP-BV curve of conscious Goldblatt hypertensive rats, the observed decrease in venous capacity was related mostly to decreased venous compliance in a one-kidney model, while there was no relation in a two-kidney model.
was seen at 5 and 8 weeks. Pan and Young\textsuperscript{27} recently demonstrated increased MCFP, due probably to expanded BV in conscious dogs with aldosterone-induced hypertension (they did not report the MCFP-BV relationship). BV expansion and MCFP elevation were much larger in their study in which the values before and during aldosterone treatment were compared in a single animal.

Expanded fluid volumes, either transient or sustained, were considerably consistent findings in mineralocorticoid-induced hypertension.\textsuperscript{25-27} In this context, such may explain why this form of hypertension is often referred to as a volume-dependent one. In contrast, CO changes were variable. A high CO state was seen in some dogs\textsuperscript{26-28} and pigs.\textsuperscript{29} Yet, when analyzing the means of a group statistically, unchanged CO and elevated TPR appeared to be more consistent hemodynamic characteristics in these animals.\textsuperscript{26-29} We were unable to find CO data in a rat model. Thus, the findings of early expanded BV and unaltered CO are compatible with those of previous studies.\textsuperscript{25-29} In view of the possibility that high CO may have been undetected in our cross-sectional study and the variability of CO itself, our findings are not sufficient to negate the "autoregulatory vasoconstriction" hypothesis that has been proposed to explain volume-dependent hypertension.\textsuperscript{30}

With regard to changes in total vascular capacity and CO, total vascular capacity was altered in the course of our DOCA-salt hypertension, as normal CO was maintained under conditions of rising blood pressure. Decreased venous capacity may be an adaptive process of the cardiovascular system in the presence of an increased afterload and perhaps hypertrophied heart, particularly when accompanied by normal or reduced BV.\textsuperscript{6, 8-10, 12, 13} We found that these vascular alterations did occur in the late stage of DOCA-salt hypertension. In our 8-week DOCA-salt rats with many features of malignant hypertension,\textsuperscript{31} decreased venous capacity seemed to be important for maintaining appropriate CO. The same has been postulated in volume-depleted Goldblatt hypertensive rats.\textsuperscript{32} On the other hand, the increased venous capacity in the 2-week DOCA-salt rats was an unexpected, but interesting finding. Because neither BV nor MAP was increased at 1 week, mild increases in BV and MAP must have been shorter than 1 week's duration, when checking at 2 weeks. At this initial stage, a dilatation of the vascular system may have occurred and hence such a mild BV expansion would have been accommodated without causing any significant increase in MCFP and perhaps CO. It is possible that volume receptor-mediated reduction in vascular tone may have contributed to the increased vascular capacity. Alternatively, baroreceptor-mediated vascular modulation might have been involved. However, in view of the lack of evident reflex bradycardia, this possibility is remote.

Concerning the arterial pressure-volume relationship, we observed a decreased systemic arterial compliance in the established and late phases of DOCA-salt rats, a result similar to that seen in SHR reported by Samar and Coleman.\textsuperscript{3} In our hypertensive rats, decreases in arterial compliance paralleled increases in TPR. The finding that changes of arterial properties (TPR and arterial compliance) preceded those of venous properties (venous capacity) may further support the secondary nature of venous capacity reduction. It is possible that decreased arterial compliance plays some role in elevating TPR by raising systolic blood pressure and therefore MAP.

Total O\textsubscript{2} consumption reflects the aerobic metabolic rate, and therefore depends primarily on muscle mass or composition, cardiovascular function or substrate availability. Walsh et al.\textsuperscript{33} detected elevated total O\textsubscript{2} consumption (expressed as per body weight) and increased arteriovenous blood O\textsubscript{2} difference in conscious SHR, although they did not identify the cause. Ferrone et al.\textsuperscript{34} found no changes in both values in awake two-kidney, two clip Goldblatt rats. Accordingly, the present finding of unaltered O\textsubscript{2} consumption and arteriovenous O\textsubscript{2} difference (table 3), indicating a normal resting metabolic rate, is consistent with observations in Goldblatt hypertensive rats.

Possible explanations for mechanisms of venous alterations have been presented in terms of: 1) increased neurogenic tone,\textsuperscript{35} 2) enhanced contractile responsiveness,\textsuperscript{4, 6, 3} changes in structural properties,\textsuperscript{5, 12} and altered water and ion composition\textsuperscript{40} or ion transport;\textsuperscript{38-39} 3) unknown humoral factors;\textsuperscript{39, 40} and so on. Interstitial tissue compliance, once considered contributory, was found to be normal in SHR\textsuperscript{10} and Goldblatt rats.\textsuperscript{22} Although we cannot make a valid comment based on our present data, the demonstration of a reduced venous capacity in the late stage of hypertension in DOCA-salt rats suggests that a pronounced enhancement of sympathetic activity and vasopressin\textsuperscript{41} and enhanced reactivity to these stimuli,\textsuperscript{3, 36} among others, may play some role.

Acknowledgments

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