Reduction in arterial compliance alters carotid baroreflex control of cardiac output in a model of hypertension

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1Department of Physiology, Harry S. Moss Heart Center, University of Texas Southwestern Medical Center, Dallas, Texas 75235; and 2Department of Biomedical Engineering, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

Potts, Jeffrey T., Kelly P. McKeown, and Artin A. Shoukas. Reduction in arterial compliance alters carotid baroreflex control of cardiac output in a model of hypertension. Am. J. Physiol. 274 (Heart Circ. Physiol. 43): H1121–H1131, 1998.—Baroreflex regulation of cardiac output is determined by the performance of the heart as well as the available blood flow returning to the heart (i.e., venous return). We hypothesized that a decrease in arterial compliance (C_a) would affect carotid baroreflex control of cardiac output by altering the slope of the venous return curve (VR curve). Baroreflex control of systemic arterial pressure (P_a), central venous pressure (P_c), heart rate, cardiac output (CO), and peripheral vascular resistance (R) were determined during bilateral carotid occlusion (BCO) in spontaneously hypertensive (hypertensive, HT) and Sprague-Dawley (normotensive, NT) rats. C_a was determined from the rate of arterial pressure decay when CO was transiently stopped, and the VR curve was obtained during gradual inflation of a vascular balloon positioned in the right atrium. The inverse slope of the VR curve was used as an index of the resistance to venous return (RVR). The baseline slope of the VR curve was −50.5 ± 3.3 vs. −35.5 ± 2.6 ml·kg⁻¹·min⁻¹·mmHg⁻¹ in NT vs. HT, respectively (P < 0.05). Control values of P_a (96 ± 5 vs. 124 ± 8 mmHg) and R (0.43 ± 0.04 vs. 0.80 ± 0.07 peripheral resistance units (PRU)) were reduced in NT, whereas C_a (0.062 ± 0.010 vs. 0.036 ± 0.003 ml·kg⁻¹·mmHg⁻¹) was elevated in NT vs. HT, respectively (P < 0.05). Analysis of the pressure dependence of C_a demonstrated that C_a was a nonlinear function of P_a, and the exponential decay constant for the C_a-P_a relationship was reduced in HT (0.0055 ± 0.0012 vs. 0.0012 ± 0.0002 min, NT vs. HT, P < 0.05). Baroreflex activation by BCO significantly increased P_a (ΔP_a 20 ± 4 vs. 28 ± 3 mmHg) and R (ΔR 0.16 ± 0.04 vs. 0.24 ± 0.06 PRU) in NT vs. HT, respectively. However, C_a significantly decreased in NT but not HT (ΔC_a −24 ± 5 vs. 4 ± 6 ml·kg⁻¹·min⁻¹, P < 0.05). In NT, RVR was increased 30% ± 9% during BCO (P < 0.05), whereas RVR increased 8% ± 3% in HT (P = NS). From these findings, we conclude that the difference in baroreflex control of CO is mediated, in part, by the reduction in C_a, which minimized the baroreflex-evoked increase in RVR.

The effect of arterial baroreceptor reflex control of capacitive vessels on cardiac output (CO) regulation, particularly reflex control of venous capacitance, is well known (5, 25, 29). However, less attention has been placed on the capacitive properties of the arterial circulation and CO regulation. Recently, we have shown that an acute increase in arterial compliance (C_a) attenuated carotid baroreflex control of CO and arterial blood pressure (P_a) (24). The mechanism mediating the reduction in baroreflex sensitivity appeared to be an alteration in the slope of the venous return curve (VR curve), namely, the resistance to venous return, which attenuated the CO response when the carotid baroreflex was activated. However, the effect of a chronic reduction in C_a, such as found in hypertension, on baroreflex control of the CO and P_a has not been shown experimentally. Furthermore, it remains unknown whether this mechanism is valid in a more chronic condition.

Changes in the resistive and capacitive properties of the arterial circulation have been well documented in hypertension (2, 3, 13, 14, 16, 20, 21, 30, 33, 35, 36). These alterations include rarefaction (3, 13, 14), changes in vessel wall thickness-to-lumen ratio, and a shift in the ratio of elastin to collagen in blood vessels (20, 35, 36). Modifications in the mechanical properties of peripheral blood vessels have also been shown to manifest changes in systemic hemodynamics. Particularly noted is the reported increase in peripheral vascular resistance, the decrease in C_a, the increase in pulse wave velocity, and the redistribution of stressed blood volume (14, 16, 18, 20, 21, 30, 34). These changes in circulatory hemodynamics result in an elevation in arterial input impedance that negatively affects left ventricular ejection and CO regulation (21).

It has been reported that a redistribution of stressed blood volume between the peripheral and central circulation improved CO regulation in a group of hypertensive patients (15, 33). These changes were attributed to the reduction in total systemic vascular capacitance that accompanied hypertension. Moreover, alterations in vascular resistance and capacitance have been reported in both human (15, 33) and animal models of hypertension (3, 14, 35, 38). Thus baroreflex control of cardiovascular function may be affected, in part, by alterations in the mechanical properties of the circulation (i.e., reductions in C_a and elevations in vascular resistance). Furthermore, these changes may contribute to the redistribution of blood volume between the arterial and venous circulation that has been previously reported (15, 33).

Recently, we reported that selectively increasing C_a attenuated carotid baroreflex control of CO in anesthetized dogs (24). In these experiments, total blood volume remained constant. Therefore, the blood volume in the systemic vascular bed could only shift between arterial and venous compartments. Because the magnitude of the baroreflex change in total peripheral resistance was not affected by the increase in C_a, we hypothesized that attenuation of the CO response was due, in part, to a greater shift in blood volume from the...
central venous circulation into the arterial circulation. This shift in central blood volume effectively reduced venous filling pressure and attenuated the CO response via the Starling mechanism. An alternative way to explain the mechanism, which is not in opposition to the above, is in terms of the VR curve and the resistance to venous return. It has been theoretically established (7) that increasing the Ca causes an increase in the resistance to venous return and consequently a decrease in venous return (i.e., the flow returning back to the heart from the periphery). The decrease in venous return, caused by the increase in resistance to venous return, would then decrease the CO. Although Guyton and co-workers (6, 8, 9) provided evidence showing that the slope of the VR curve remained constant during baroreflex activation because of the opposing effects of the carotid baroreceptor reflex on peripheral resistance and vascular compliance. Moreover, Hatanaka et al. (11) used a lumped four-parameter model of the systemic circulation to determine whether an acute increase in Ca altered baroreflex control of CO by changing the slope of the VR curve. When Ca was acutely increased, they reported that the baroreflex-evoked change in CO and Pa was attenuated. This effect was ascribed to an increase in the resistance to venous return. The elevation in the resistance to venous return effectively attenuated the changes in CO without affecting other baroreflex-controlled variables (i.e., reflex changes in heart rate and peripheral vascular resistance). Taken together, these studies (5, 11, 24) suggest that the relationship between Ca and peripheral vascular resistance may be important in Pa regulation and baroreflex control of CO.

The purpose of the present study was to determine if a chronic reduction in Ca, such as found in experimental models of hypertension, may alter baroreflex control of CO. We reasoned that if acutely increasing the Ca increased the resistance to venous return, the converse may also be true. Furthermore, it was proposed that it did not matter if the differences of Ca were acutely instilled or if they existed chronically. Baroreflex changes in CO were compared between normotensive Sprague-Dawley (SD) rats and spontaneously hypertensive (SHR) rats characterized by genetically different levels of Ca and total peripheral resistance (16, 20). We hypothesized that a reduction in Ca in SHR would maintain CO during bilateral carotid occlusion (BCO) and thus preserve baroreflex control of Pa despite the elevation in basal peripheral vascular resistance. The influence of a chronic elevation in vascular resistance and a reduction in vascular compliance on baroreflex control of CO was evaluated by measuring the VR curve in the presence and absence of BCO. The slope of the VR curve and the resistance to venous return (1/slope) were used as indexes of the affect of vascular resistance and compliance on baroreflex control of CO in normotensive (NT) and hypertensive (HT) rats. A preliminary report of these findings has been previously published (23).

METHODS

Surgical procedures. Fifteen- to twenty-five-week-old SD rats (Charles River) and SHR rats (Taconic) (431 ± 27 vs. 352 ± 10 g, respectively) were anesthetized with an intramuscular injection of a mixture of ketamine (120 mg/kg) and acepromazine (50 µg/kg). Body temperature was maintained at 37°C by a heated water-perfused surgical platform. Catheters (PE-50, Intramedic) were inserted into the femoral artery to record Pa and the inferior vena cava via the femoral vein to record central venous pressure (Pv). Both catheters were advanced ~3 cm in the cephalad direction so that their tips were in the central circulation. These catheters were connected to pressure transducers (Statham P23 Db and P23 BB) to monitor Pa and Pv, respectively. Placement of the central venous catheter was confirmed at the termination of each experiment by direct visual inspection. Supplemental anesthesia was administered when required.

A midline incision was made on the ventral surface of the neck extending to the sternum. The skin was retracted using silk ties, two posteriorly and two anteriorly. The overlying fat and connective tissue from the masseter muscle to the sternum were cleared by blunt dissection. The sternohyoideus was carefully separated longitudinally to expose the trachea, and a polyethylene catheter (PE-240, Intramedic) was inserted. A vascular balloon (4-F Fogarty, Baxter Healthcare, Santa Ana, CA) was carefully advanced to the junction of the caval veins and the right atrium by the right external jugular vein. Placement of the vascular balloon was confirmed by visual inspection at the end of each experiment.

The common carotid arteries were isolated by retracting the sternohyoideus and sternomastoideus and carefully cauterizing the omohyoideus. This approach exposed the common carotid artery and the carotid bifurcation. Ligatures were placed around the cervical vagosympathetic trunk bilaterally, and the nerves were tied and transected to eliminate the buffering capacity of the aortic and cardiopulmonary baroreceptors. Finally, a vascular occluder (2 mm ID, In Vivo Metrics, Healdsburg, CA) was placed around each common carotid artery ~1 cm proximal to the carotid bifurcation. Bipap inflation of the vascular occluders temporarily decreased carotid sinus pressure to activate the carotid sinus baroreceptor reflex.

The chest was opened using a right lateral thoracotomy at the level of the second or third intercostal space, and the rat was placed on a mechanical ventilator. A small retractor was used to separate the ribs to expose the heart, and the thymus gland was reflected to expose the ascending aorta. The aorta was carefully dissected free of surrounding adipose and connective tissues until the region was clear and the aorta was accessible. An ultrasonic transit-time flow probe (2.0 or 2.5 mm, Transonic Systems, Ithaca, NY) was positioned around the ascending aorta, and ultrasound gel (Sonostat, Lewistown, PA) was used to ensure adequate coupling and signal quality. The thoracotomy was then closed with 3-0 sutures; however, the pneumothorax was not reduced. Mechanical ventilation was continued with supplemental oxygen through the remainder of the experiment, and blood gases were measured to determine the adequacy of ventilation.

Experimental protocols. Carotid sinus baroreflex function was first assessed by BCO and steady-state reflex changes in Pa, Pv, and CO (~2 min after initiation of common carotid artery occlusion) were recorded. Reflex changes in peripheral vascular resistance (R) were calculated as (Pa−Pv)/CO and
expressed in peripheral resistance units (PRU; mmHg·ml⁻¹·min⁻¹·kg⁻¹). The effect of the intrinsic mechanical properties of the peripheral circulation on venous return and CO was characterized by measuring the slope of the VR curve.

RESULTS

Baseline hemodynamics and responses to BCO. A summary of the baseline hemodynamics and the reflex responses to BCO are presented in Fig. 1 (see also Table 1). In HT rats, baseline mean Pa and R were increased and CO was reduced (P < 0.05). However, there was no significant difference in baseline heart rate (HR) or stroke volume (SV), although both HR (399 vs. 356 beats/min) and SV (0.58 vs. 0.53 ml/kg) were larger in NT vs. HT rats, respectively. Clamping the common carotid arteries increased Pa and R in both strains of rat. However, the reflex change in CO differed considerably between groups. BCO consistently decreased CO in NT rats, whereas CO increased or remained unchanged in HT rats. The reflex HR responses to BCO were similar between the two strains (P = NS). However, SV decreased 16% in NT rats, whereas in HT rats, SV decreased only 4% (NT vs. HT, P < 0.05).

Correlation analyses were computed to determine the effect of Pa or, as well as the reflex changes on Pa and R, on the CO response during BCO (see Table 2). No significant relationships were found between ΔCO·ΔPa (F = 0.75, r = 0.23, P = 0.40) or between ΔCO·ΔR (F = 0.66, r = 0.21, P = 0.43). However, there was a significant correlation in CO differed considerably between groups. BCO consistently decreased CO in NT rats, whereas CO increased or remained unchanged in HT rats. The reflex HR responses to BCO were similar between the two strains (P = NS). However, SV decreased 16% in NT rats, whereas in HT rats, SV decreased only 4% (NT vs. HT, P < 0.05).

Measurement of Cao, Cao, and determination of the pressure dependence of Cao. In a subset of animals (useable data were available from 5 NT and 3 HT animals from each group), Cao was estimated from the rate of Pa decay when CO was temporarily reduced to zero using the stop-flow method. An original trace illustrating the hemodynamic responses is shown in...
Fig. 1. Summary data showing baseline (open bars) and reflex responses to bilateral carotid occlusion (solid bars) for systemic arterial pressure (SAP), cardiac output (CO), peripheral vascular resistance (PVR), peripheral resistance units (PRU), heart rate (HR), and stroke volume (SV) in normotensive (NT) and hypertensive (HT) rats \( (n = 8 \text{ for NT and HT}) \). *Significant difference from baseline \( (P < 0.05) \). **Significant difference between NT and HT \( (P < 0.05) \).

Fig. 2. Rapid balloon inflation reduced CO to zero over 2–3 s, and \( P_a \) fell to a steady-state zero-flow pressure within 10–15 s. \( C_a \) was calculated using a monoexponential pressure decay method during the stop-flow procedure. The variables derived from these analyses are listed in Table 3. Arterial pressure \( (P_a) \) and arterial resistance \( (R_a) \) before the stop-flow procedure were greater in HT rats, whereas the derived rate constant for arterial pressure decay \( (\tau) \) as well as the calculated \( C_a \) were reduced \( (P < 0.05) \). Although the zero-flow arterial pressure \( (P_{a,0}) \) tended to be greater in HT rats, no significant difference was found between the two rat strains.

Results from the nonlinear analysis of the effect of \( P_a \) on \( C_a \) is also shown in Table 3 and Fig. 3. To generate these data, a series of small volume changes \( (0.5 \text{ ml}) \) was used to increase and decrease \( P_a \). \( C_a \) was then determined using the stop-flow method. With this approach, \( P_a \) was altered over a wide pressure range \( (75–100 \text{ mmHg}) \) to determine the pressure dependence of \( C_a \). Several points can be made from these data. First, the nonlinear model used to assess the pressure dependence of \( C_a \) was appropriate \( (17) \). This was substantiated by a significant difference in the exponential decay constant \( (\alpha) \) between NT and HT rats \( (0.0055 \text{ vs. } 0.0012 \text{ min, respectively}; \ P < 0.05) \). Furthermore, the predicted level of \( C_a \) at \( P_a \) values of 0 mmHg \( (C_a(0)) \) and 250 mmHg \( (C_a(250)) \) also approached significance \( \text{[Ca}(250), T = 2.4, P = 0.09; C_a(250), T = 2.2, P = 0.08 \text{.} \) Therefore, there was a quantitative difference in the \( C_a-P_a \) relationship between NT and HT rats. These findings suggest that the difference in \( C_a \) between NT and HT was not due exclusively to the level of \( P_a \).

Steady-state levels of venous pressure were plotted with the corresponding change in blood volume during the stop-flow procedure to determine the lumped venous pressure-volume \( (P-V) \) relationship. Data obtained from 5 NT and 3 HT rats are illustrated in Fig. 4. The derived slope of the venous \( P-V \) relationship for NT and HT rats was 1.54 and 1.06 ml/mmHg, respectively. The correlation coefficients \( (r^2) \) for the goodness of fit

Table 1. Summary of baseline hemodynamics and the effect of bilateral carotid occlusion in normotensive and spontaneously hypertensive rats

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<tr>
<th></th>
<th>Normotensive</th>
<th>Hypertensive</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>BCO</td>
</tr>
<tr>
<td>( P_a ), mmHg</td>
<td>96 ± 5</td>
<td>122 ± 6†</td>
</tr>
<tr>
<td>( P_v ), mmHg</td>
<td>3.2 ± 0.4</td>
<td>3.1 ± 0.3</td>
</tr>
<tr>
<td>( CO ), ml·min(^{-1}·kg(^{-1})</td>
<td>241 ± 19</td>
<td>216 ± 20†</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>399 ± 16</td>
<td>406 ± 16†</td>
</tr>
<tr>
<td>SV, ml/kg</td>
<td>0.58 ± 0.06</td>
<td>0.50 ± 0.05†</td>
</tr>
<tr>
<td>( R), PRU</td>
<td>0.43 ± 0.04</td>
<td>0.59 ± 0.07†</td>
</tr>
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</table>

Values are means ± SE of 8 rats each for normotensive and hypertensive groups. BCO, bilateral carotid occlusion; %change, percent change from control; \( P_a \), arterial blood pressure; \( P_v \), central venous pressure; \( CO \), cardiac output; HR, heart rate; SV, stroke volume; \( R \), peripheral vascular resistance; PRU, peripheral resistance units. *Significantly different from normotensive control \( (P < 0.05) \). †Significantly different from control \( (P < 0.05) \).
were 0.8934 and 0.8631 for NT and HT rats, respectively. From the slope, we estimated that $C_v$ was reduced by 20% reduction in HT rats (3.6 vs. 3.0 ml·kg\(^{-1}\)·mmHg\(^{-1}\), NT vs. HT).

Effect of BCO on VR curve. An example of the hemodynamic responses to graded right atrial occlusion obtained from one NT and one HT rat are illustrated in Figs. 5 and 6, respectively. Baseline $P_a$ was lower (110 vs. 150 mmHg) and CO higher (275 vs. 225 ml·kg\(^{-1}\)·min\(^{-1}\)) in NT vs. HT. Baseline central venous pressure (3.0 vs. 2.5 mmHg) was similar in NT and HT rats. During control, graded balloon inflation reduced systemic $P_a$ and CO and increased $P_v$. BCO (shown by the stippled bars) reduced CO 20% in NT (275 to 225 ml·kg\(^{-1}\)·min\(^{-1}\), $P < 0.05$). In comparison, CO decreased 4% in HT (225 to 215 ml·kg\(^{-1}\)·min\(^{-1}\), $P = NS$).

Figure 7 illustrates the VR curve constructed from the data presented in Figs. 5 and 6. Graded balloon inflation was well tolerated by all animals, and the hemodynamic responses were very reproducible. The relationship between VR and $P_v$ was essentially linear over a wide range of CO and $P_v$ values. The coefficients of determination ($r^2$) for the VR curves obtained from least-squares linear regression ranged between 0.9360 and 0.9992, and an average value of 0.9839 ± 0.0173 was obtained. Although baseline CO was similar in these two rats, the slope of the VR curve was steeper in NT rats (−58.1 ml·kg\(^{-1}\)·min\(^{-1}\)·mmHg\(^{-1}\)) than in HT rats (−39.2 ml·kg\(^{-1}\)·min\(^{-1}\)·mmHg\(^{-1}\)). A summary of the baseline hemodynamics and the effect of BCO on parameters used to describe the VR curve are presented in Table 4. BCO decreased the slope of the VR curve 28% in NT rats compared with 7% in HT rats ($t = 3.0$, $P = 0.018$). The reduction in slope corresponded to 39% increase in RVR in NT rats compared with 8% in HT rats ($t = 3.0$, $P = 0.018$). This difference in baroreflex control of the VR curve and CO occurred despite similar reflex changes in $P_a$, HR, and R (see Table 1). The zero-flow pressure intercept of the VR curve, used as an index of $P_{md}$, was similar between NT and HT animals ($t = 0.14$, $P = 0.89$). BCO did not affect $P_{md}$ ($P = NS$).

DISCUSSION

The purpose of this study was to determine whether genetic alterations in resistive and capacitive properties of the arterial circulation altered carotid baroreflex control of CO. We used the SHR as a model to study

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**Table 2.** Correlation analyses between baroreflex changes in cardiac output, arterial blood pressure, peripheral vascular resistance, and level of arterial compliance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Slope</th>
<th>Intercept</th>
<th>r value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta CO-\Delta P_a$</td>
<td>0.4 ± 0.5</td>
<td>-24 ± 12</td>
<td>0.2252</td>
<td>0.4017</td>
</tr>
<tr>
<td>$\Delta CO-\Delta P$</td>
<td>-30 ± 36</td>
<td>-8 ± 9</td>
<td>0.2128</td>
<td>0.4288</td>
</tr>
<tr>
<td>$\Delta CO-P_v$</td>
<td>-478 ± 162*</td>
<td>4 ± 8</td>
<td>0.7219</td>
<td>0.0184</td>
</tr>
</tbody>
</table>

Values are means ± SE of 10 rats (normotensive, $n = 5$; hypertensive, $n = 5$). CO, cardiac output (ml·kg\(^{-1}\)·min\(^{-1}\)); $P_a$, arterial pressure (mmHg); $R_v$, peripheral vascular resistance (PRU); $C_a$, arterial compliance (ml·kg\(^{-1}\)·mmHg\(^{-1}\)). *Significant difference ($P < 0.05$).

**Table 3.** Variables used to calculate arterial compliance and pressure dependence of arterial compliance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive</th>
<th>Hypertensive</th>
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<tr>
<td>$P_a$, mmHg</td>
<td>91 ± 4</td>
<td>117 ± 12*</td>
</tr>
<tr>
<td>$P_{mdf}$, mmHg</td>
<td>17 ± 2</td>
<td>20 ± 1</td>
</tr>
<tr>
<td>$\tau$, min</td>
<td>0.0270 ± 0.0029</td>
<td>0.0256 ± 0.0023*</td>
</tr>
<tr>
<td>$R_v$, units</td>
<td>0.50 ± 0.09</td>
<td>0.74 ± 0.11*</td>
</tr>
<tr>
<td>$C_a$, units</td>
<td>0.0618 ± 0.0100</td>
<td>0.0360 ± 0.0033*</td>
</tr>
</tbody>
</table>

Values are means ± SE of 5 normotensive and 3 hypertensive rats. $P_a$, arterial pressure before stop-flow procedure; $P_{mdf}$, zero-flow arterial pressure; $\tau$, rate constant of arterial pressure decay; $R_v$, arterial resistance (mmHg·ml·kg\(^{-1}\)); $C_a$, estimate of arterial compliance (ml·kg\(^{-1}\)·mmHg\(^{-1}\)); $C_v(0)$, model estimate of arterial compliance at arterial pressure of 0 mmHg; $C_v(250)$, model estimate of arterial compliance at arterial pressure of 250 mmHg; $\lambda$, exponential decay constant for arterial pressure-compliance relationship. See METHODS for equations used to calculate $C_v$. *Significant difference between normotensive and hypertensive ($P < 0.05$). †Difference between normotensive and hypertensive ($P = 0.09$). ‡Difference between normotensive and hypertensive ($P = 0.08$).
these effects because these animals are characterized by reductions in vascular compliance and elevations in vascular resistance. In the present study, the level of $C_a$ was significantly reduced in SHR. The reduction in $C_a$ was due, in part, to a decrease in the mechanical distensibility of the arterial compartment as indicated by the difference in the $C_a$-$P_a$ relationship (see Fig. 3). BCO produced vastly different changes in the slope of the VR curve in NT vs. HT rats. In NT, BCO significantly decreased the slope, increased RVR, and decreased CO 11%. In contrast, BCO did not alter the slope of the VR curve, RVR, or CO in HT rats. Changes in SV, calculated from the CO and HR responses, also differed between strains. SV decreased 16% in NT compared with only a 4% reduction in HT rats. Taken together, these findings support the hypothesis that changes in vascular resistance and compliance can alter baroreflex control of VR and CO in NT and HT, despite no apparent difference in the pumping ability of the heart.

Baseline levels of CO and the slope of the VR curve were significantly reduced in HT compared with NT animals. The reason behind this finding is not readily apparent. Our finding is in agreement with Levy et al. (16), who reported that baseline CO was reduced in SHR compared with NT control rats. However, the level of CO in their study was lower than the CO reported in our study. This difference may have been because of the depressive actions of pentobarbital sodium that was used in the study of Levy et al. (16). A reduction in baseline CO is also supported by Pfeffer et al. (22), who investigated the effect of aging on cardiac function in different strains of NT and HT rats. However, they reported that the peak pumping ability of the left ventricle (assessed by rapid infusion of Tyrode solution) did not differ between strains and was only decreased in SHR at 52 wk of age. These data suggest that the pumping ability of the left ventricle was not compromised in SHR of 15–25 wk of age. Therefore, myocardial dysfunction cannot explain the differences in CO between NT and HT rats in the present study.

In addition to the heart itself, the volume of blood returning to the heart (i.e., venous return) plays an important role in determining steady-state CO. Guyton and co-workers (6, 8, 9) developed the concept of using venous return and cardiac function curves to determine the relative contribution of peripheral and cardiac factors that determine steady-state CO. They considered the inverse slope of the VR curve a measure of the resistance to venous return and have reported that for any given pressure gradient venous return is inversely proportional to the quantitative value of its slope. The inverse slope of the VR curve represents the algebraic sum of all the peripheral resistances weighted proportionally to the compliance of individual circulatory beds (6). Moreover, it has been demonstrated that reflex changes in total peripheral resistance and peripheral vascular compliance (arterial and venous) exert opposing affects on the slope of the VR curve (5, 11). These studies demonstrated that an increase in peripheral vascular resistance reduced venous return, whereas a
decrease in vascular compliance increased venous return and steady-state CO in the absence of changes in cardiac function.

In the present study, the baseline level of peripheral vascular resistance and total systemic $C_a$ were significantly different between the two rat strains. Peripheral vascular resistance in HT rats was approximately twice as large as the measured level in NT rats. This finding is supported by a number of previous studies (1, 3, 14, 20, 21, 26). If left ventricular afterload was a critical...
Fig. 7. Example of venous return curve from a normotensive (A) and hypertensive (B) rat during control (○) and BCO (●). Venous return curves were obtained from data in Figs. 5 and 6. BCO decreased slope of venous return curve 25% in normotensive rats vs. 5% reduction in hypertensive rat. Note steeper slope of venous return curves in normotensive rat.

Table 4. Effect of BCO on parameters describing venous return curve

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<th>Hypertensive</th>
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<tr>
<td></td>
<td>Control</td>
<td>BCO</td>
</tr>
<tr>
<td>VR slope, mmHg/PRU</td>
<td>−50±3</td>
<td>−37±3*</td>
</tr>
<tr>
<td>RVR, mmHg/m²·kg·min</td>
<td>0.021±0.002</td>
<td>0.028±0.002*</td>
</tr>
<tr>
<td>Pmcf, mmHg</td>
<td>7.4±0.3</td>
<td>7.8±0.5</td>
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Values are means ± SE of 7 normotensive and 5 hypertensive rats. VR slope, derived slope of venous return curve; RVR, calculated resistance of venous return (1/VR slope); Pmcf, estimate of mean circulatory filling pressure. *Significant different between control and BCO (P < 0.05). †Significant difference between normotensive and hypertensive rat (P < 0.05).

factor in determining venous return and CO, then the significant elevation in baseline vascular resistance should have a negative influence on the heart (and on venous return). However, despite the elevation in baseline resistance in HT animals, venous return and CO were affected to a lesser degree during BCO. Our model suggests that this effect is due, in part, to the reduction in Ca in HT that favored venous return.

Of particular interest to the present study, the level of Ca was also significantly reduced in SHR. From the correlation analyses (see Table 2), we can estimate that the difference in Ca may account for ∼50% of the CO response elicited by BCO. A significant reduction in Ca in SHR is in general agreement with the findings of Samar and Coleman (27). In their study, Ca was determined by measuring the change in Pa produced by small, rapid changes in arterial blood volume when blood flow through the arterial circuit was zero. However, because this approach was different from the modeling approach used in our study, it is not possible to determine whether the difference in Ca reported by Samar and Coleman (27) was because of a change in the distensibility of arterial blood vessels, or whether it occurred passively as a result of the elevated Pa in SHR.

To determine the passive effect of Pa on total systemic Ca, we repeatedly measured Ca while varying the level of Pa over 100 mmHg (see Fig. 3 and Table 3). Several important features should be gleaned from these data: 1) the relationship between Pa and total systemic Ca is nonlinear in both NT and HT rats; 2) at any level of Pa, the total systemic Ca was found to be lower in HT rats; and 3) because the exponential decay constant for the Ca-Pa relationship was significantly reduced in HT rats, it follows that for a given increase in Pa the accompanying increase in stressed arterial blood volume must also be reduced in HT rats. Therefore, our findings show that the arterial compartment in HT animals was ∼60% less compliant than their NT counterpart. Furthermore, we have shown that the reduction in Ca appears to be independent of the higher blood pressure in HT rats.

Several different approaches have been developed to estimate total Ca (31, 37). We chose a nonlinear equation to fit these data over the wide range in Pa values because a linear fit was not acceptable. This is contrary to the reported findings from Samar and Coleman (27). They reported that over a smaller pressure range (7–40 mmHg), the pressure-volume relationship of the arterial compartment was essentially linear. It is reasonable to assume that larger changes in Pa are required to exhibit the nonlinear behavior on the Pa-volume relationship. It is known that Ca is a nonlinear exponential function of Pa (17). With the use of a nonlinear model to assess the pressure dependence of Ca, it was concluded that over a wide range of Pa (50–180 mmHg), the compliance of the arterial bed was reduced in SHR.

In addition to a reduction in Ca, a decrease in the capacitive properties of the venous compartment has also been reported in hypertension. Greenburg and Bohr (4) found that the distensibility of portal vein strips in SHR was reduced when compared with normotensive controls. Simon (30) compared the upper body and lower body venous pressure-volume relationship in SHR and NT controls. In SHR, they reported that the venous pressure-volume relationship was shifted down toward the pressure axis showing that the slope of the pressure-volume relationship was reduced in hypertension. However, it was not possible to discern whether these changes in pressure-volume relationship were because of alterations in venous compliance, un-stressed venous volume, or both. Samar and Coleman (27) used the relationship between Pmcf and blood volume to evaluate whole body venous compliance and unstressed volume. They also reported a shift in the Pmcf-blood volume curve toward the pressure axis in
SHR. This shift was similar to the pressure-volume shift reported by Simon (30). However, within a range of $P_{mf}$ (4–12 mmHg), they found no difference in whole body venous compliance. Therefore, they explained the shift in the pressure-volume curve by a decrease in unstressed volume in SHR.

We also found a difference in the venous pressure-volume relationship between NT and HT animals when vascular volume was changed (see Fig. 4). The values for lumped venous compliance are in general agreement with those reported by Samar and Coleman (27). Although this approach constitutes a rough estimate of venous compliance, the effect of a change in the unstressed venous volume cannot be directly determined. Furthermore, the contribution that this reduction in $C_v$ may have exerted on the slope of the VR curve was not directly assessed in the present study. However, because the resistance to venous return is given by the product of $[C_v/(C_a + C_v)]\cdot R$, it follows that a decrease in $C_v$ would increase the $[C_a/(C_a + C_v)]$ ratio and increase the RVR. Therefore, our model predicts that a reduction in $C_v$ would negatively affect venous return and CO during BCO.

Proposed mechanism. The aorta and large arteries serve not only as conduit vessels but also as a blood storage compartment. Furthermore, the elastic properties of blood vessels, and the higher intravascular pressure in arteries, enable large arteries to accumulate and store a considerable blood volume ($V_a$). Because of the nonlinearity of the $P_a$-volume relationship (17), the magnitude of $V_a$ will depend on the pressure in the compartment ($P_a$), the compliance of the arterial compartment ($\Delta V_a/\Delta P_a$), and the arterial unstressed volume. Therefore, any increase or decrease in $P_a$ must be associated with a concomitant increase or decrease in blood volume in the arterial compartment. We have proposed a lumped-parameter model of the circulation to illustrate the potential impact that a reduction in $C_a$ may have on the mobilization of blood volume (see Fig. 8). Distributed models may be more accurate in predicting the changes in pressure, flow, and the redistribution of blood volume between specific vascular beds, but there exists a problem. In most instances, we do not know the absolute parameter values or even the relative changes in these parameters. Therefore, although the structure of a distributed model may be more appropriate, the parameter values cannot be experimentally confirmed. Thus the principal reason for the popularity of lumped-parameter models is that one can determine the parameter values and then use them to predict the gross hemodynamic features of the circulation (8, 11, 24, 28, 29).

The lumped-parameter model presented here is a representation of the peripheral circulation consisting of an arterial compartment, a venous compartment, and a variable peripheral resistor. For our discussion concerning the importance of $C_a$ on CO regulation, we have replaced the heart with a fixed-rate flow pump and have included a venous volume reservoir. This model has been extensively used by Shoukas and Sagawa (29) to demonstrate the importance of carotid baroreflex control of venous capacitance in CO regulation. A modification of the Shoukas-Sagawa model illustrates how this model has been adapted to reflect the hemodynamic changes reported in hypertension. Several features of this model should be noted. First,
the cross-sectional area of each compartment reflects the compliance of that compartment, in so much as a change in pressure is accompanied by a change in stressed volume. The cross-sectional area in the hypertensive model has been reduced 50% to reflect the decrease in Ca (16, 21, 26, 27). Second, constriction of the tube between the arterial and venous compartments represents the peripheral vascular resistance. Note that in the hypertensive model this constriction is larger than in the normotensive model. This has been done to reflect the elevation in vascular resistance found in SHR (21). Third, the height of each fluid column indicates the blood pressure in each compartment. Finally, we have set the flow rate and venous column indicates the blood pressure in each compartment. Thus, at any given flow rate, the Pa in the hypertensive model will be elevated.

To determine the effect of a decrease in Ca on venous return, we increased vascular resistance equal amounts in both models. Under this condition, the increase in Pa must be proportional to the increase in R. Our data indicated that the baroreflex-induced increase in vascular resistance was similar in the two rat strains (37 vs. 28%, NT vs. HT, respectively). Therefore, when R was increased to the same degree in both the NT and HT model, our model predicted that Pa would increase a similar amount (20 vs. 23%, respectively). However, despite similar increases in pressure, a greater fall in reservoir volume was predicted in the NT model. This volume was pumped out of the venous reservoir and into the arterial compartment by the fixed-rate pump to generate the increase in Pa. The magnitude of this volume shift was dependent on the pressure-volume relationship (i.e., compliance) of the arterial compartment. The decrease in venous volume in this model is analogous to a decrease in central blood volume in an intact animal. If central blood volume is reduced, this may lead to a decrease in end-diastolic volume and shift down the Starling curve. Thus, in the present study, the decrease in SV in NT during BCO may have resulted from a greater increase in arterial volume due to the larger Ca. This may explain the difference in CO regulation found in this study and reported elsewhere (7, 11, 12, 19, 32).

Limitations. Because the outflow tract of the left ventricle was not occluded during the stop-flow procedure and the heart continued to beat, the decay rate of the downstream Pa was lengthened, and this would lead to an overestimation of Ca. This would certainly pose a problem if there was a difference in the cardiopulmonary blood volume between NT and HT rats. However, it is not known whether such a difference exists. It has been reported that cardiopulmonary blood volume is larger in essential and renovascular HT patients compared with aged-matched NT controls (15, 33). If this were also the case in HT rats, then a larger blood volume would have been pumped into the arterial circulation during the stop-flow procedure. This larger blood volume would have increased the time constant for Pa decay and resulted in a larger Ca in the HT animals (because Ca was calculated as τ/Ra). Therefore, because we reported that Ca was reduced 50% in HT rats in the absence of clamping the ascending aorta, it is likely that the actual difference in total systemic Ca between NT and HT animals was larger than the 50% difference reported in the present study.

Lack of complete vascular isolation of the carotid sinuses may have resulted in further deactivation of the carotid baroreceptor reflex during graded occlusion of the right atrium. However, it is unlikely that this altered our results or our interpretation of these experiments for the following two reasons. First, BCO decreases sinus pressure close to, or below, the threshold pressure for the baroreflex. Furthermore, carotid sinus pressure must follow the progressive reduction in Pa during the balloon inflation procedure. Therefore, carotid sinus pressure should remain well below the minimal threshold pressure required to activate the reflex when the VR curve was measured during BCO. Second, we have repeated these experiments in rats after vascular isolation and constant perfusion of the carotid sinus regions. We found that the slope of the VR curve in a normotensive rat was decreased to a similar degree when the carotid sinus regions were isolated and perfused at constant pressure as when the baroreflex was activated by BCO (Potts and Shoukas, unpublished observations).

In summary, hypertension is known to alter CO regulation by decreasing myocardial function and increasing the resistive properties of the peripheral circulation. In addition to these factors, the present study demonstrated that a reduction in Ca decreased the resistance to venous return in an experimental model of hypertension. It is proposed that the difference in Ca may have contributed to the difference in CO regulation by shifting the volume of blood between the arterial and venous circulation. A theoretical model has been proposed to predict how a reduction in Ca may alter the distribution of blood volume.

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**REFERENCES**


