Venous Tone in the Developmental Stages of Spontaneous Hypertension

Douglas S. Martin, Manoj C. Rodrigo, Christopher W. Appelt

Abstract—The initial stages of hypertension in the spontaneously hypertensive rat (SHR) are characterized by an increase in cardiac output. Venous capacitance plays an important role in the control of cardiac output. This study tested the hypothesis that venous tone is elevated in the developmental stages of spontaneous hypertension. Male SHR or normotensive Wistar-Kyoto (WKY) rats were instrumented for the measurement of arterial pressure (FAP) and intrathoracic vena caval pressure (FVP). A latex-tipped catheter was advanced into the right atrium via the jugular vein. Mean circulatory filling pressure (MCFP), an index of integrated venomotor tone, was calculated as MCFP=FVP+(FAP−FVP)/VAR. FAP and FVP were recorded after 5 seconds of right atrial balloon inflation. The venous to arterial compliance ratio (VAR) was estimated as 76 for WKY and 106 for SHR. Mean arterial pressure (MAP), heart rate, and MCFP were recorded in conscious rats of 4 to 6 and 8 to 10 weeks of age. In 4- to 6-week-old rats, both MAP and MCFP were significantly elevated in the SHR (MAP, 129±6 mm Hg; MCFP, 6.6±0.4 mm Hg) compared with the age-matched WKY (MAP, 91±6 mm Hg; MCFP, 5.4±0.4 mm Hg), whereas heart rate was not significantly different. The elevations in MAP (SHR, 144±4 mm Hg; WKY, 102±3 mm Hg) and MCFP (SHR, 7.7±0.3 mm Hg; WKY, 6.0±0.2 mm Hg) in SHR were exaggerated at 8 to 10 weeks of age. After ganglionic blockade (chlorisondamine; 10 mg/kg), the differences in MCFP were no longer statistically significant between SHR and WKY at both 4 to 6 weeks of age (3.9±0.2 versus 4.0±0.3 mm Hg) and 8 to 10 weeks of age (5.0±0.3 versus 4.3±0.3 mm Hg, respectively). The differences in MAP at 4 to 6 weeks of age (79±7 versus 67±5 mm Hg, respectively) also were not statistically significant after ganglionic blockade. However, a significant difference in MAP between strains remained after ganglionic blockade in 8- to 10-week-old rats (90±5 versus 63±3 mm Hg, respectively). These findings indicate that venous tone is increased via autonomic effector systems during the developmental stages of spontaneous hypertension. These data also suggest that autonomic mechanisms predominate at very early stages, whereas nonautonomic mechanisms assume more importance in maintaining the elevated MAP as hypertension progresses. (Hypertension. 1998;31[part 1]:139-144.)

Key Words: veins ▪ blood pressure ▪ hypertension, spontaneous ▪ venous pressure

It is clear that hypertension is a multifactorial disease. Nevertheless, hemodynamic considerations indicate that arterial blood pressure is a function of TPR and CO. Therefore, hypertension, regardless of the underlying mechanism must be the result of an increase in TPR, CO, or a combination of both. The initial stages of the hypertensive process in both animals and humans are characterized by an increase in CO. Increases in CO have been observed in the developmental stage of several forms of experimental renal hypertension.1,2 Similarly, CO is elevated at an early age in the SHR.3,4 In humans, up to 50% of borderline hypertensive subjects have an elevated CO.5 The elevation in CO is transient. In the established phase of the disease, hypertension is maintained by an elevated TPR and normal CO.6 There are several mechanisms that may account for the elevated TPR during this stage of spontaneous hypertension including metabolic7,8 or myogenic6 responses to the initial increase in CO. Therefore, an increase in CO may be an important initiating factor in some forms of animal and human hypertension. A better understanding of the factors that contribute to the initial increases in CO observed in hypertensive subjects should provide insight into the initiation of the hypertensive process.

The factors controlling CO are complex and include HR, cardiac contractility, preload, and afterload. However, under any given hemodynamic conditions at equilibrium, CO must equal venous return. The interdependence of CO and venous return has been clearly delineated.9,10 Venous return is governed by the resistance to and the pressure gradient for blood flow to the right atrium. All components of the cardiovascular system contribute to the control of venous return. However, because 60% to 75% of the total blood volume is contained in the veins, on a quantitative basis changes in venous capacitance play a major role in the control of venous return and CO.9,11 Recently, simultaneous determinations of cardiac function and venous return curves in dogs have shown that a maximal reflex change in venous capacitance could alter CO by up to 40%.12 Thus, changes in venous function have important implications for the control of CO and cardiovascular homeostasis. Accord-
ingly, it is possible that changes in venous capacitance may contribute to the initial increases in CO observed during the development of hypertension.

A reduction in venous capacitance has been implicated in the etiology of hypertension. MCFP, an index of venous constrictor tone and blood volume, is elevated in dogs subjected to renal wrap and in the Goldblatt and SHR hypertensive models. No changes in blood volume were observed in these studies, suggesting that the elevated MCFP was due primarily to active venoconstriction. Decreases in both unstressed vascular volume and compliance have been recorded in these models. Venous compliance is also reduced in perinephritic hypertension in dogs and in essential hypertension in humans. In both animal and human hypertension, the decreases in venous capacitance occurred preferentially in the systemic veins and favored an increase in cardiopulmonary volume and CO. Thus, there is convincing evidence that venous tone is increased in various models of hypertension. However, these studies have primarily examined the established phase of hypertension. Accordingly, it is not clear whether elevations in venous tone participate in the developmental stages of hypertension. The present study was undertaken to test the hypothesis that neurogenically mediated increases in peripheral venous tone occur early in the development of hypertension in the SHR.

Methods

Animals
Male SHR (n=19) and WKY (n=14) rats were purchased from Taconic Farms (German Town, NY) at 4 weeks of age and maintained in the vivarium at the University of South Dakota. The animals were maintained on a 12-hour day/night cycle and were allowed free access to standard laboratory rat chow and tap water. The rats were used for experiments in two age groups: 4 to 6 weeks of age and 8 to 10 weeks of age. The institutional animal care and use committee reviewed and approved all procedures involving these animals.

Surgeries
Two days before experimentation, the rats were anesthetized with an intraperitoneal injection of pentobarbital sodium (60 mg/kg) and atropine (0.4 mg/kg). Cannulas were implanted into the left femoral artery (tygon 0.06-in OD tipped with 28-gauge polytetrafluoroethylene) and vein (tygon 0.06-in OD tipped with 0.04-in OD microcathonel) for the measurement of mean arterial pressure and central venous pressure, respectively. The venous catheter was advanced to the thoracic portion of the inferior vena cava. A small latex balloon was advanced into the right atrium through the right jugular vein. Proper positioning of the balloon was determined empirically at the time of surgery as the position at which balloon inflation produced a rapid smooth decrease in arterial pressure and a cessation of arterial pulsations. All catheters were filled with heparinized saline (25 mL/mL) and exteriorized to the tape of the neck. The rats were allowed to recover for 48 hours during which time they were acclimatized to the recording environment.

Measurement of MCFP
MCFP was used to estimate integrated venomotor tone. MCFP is a reliable means of estimating the overall degree of venous tone that is especially applicable to the conscious animal. MCFP can be determined by recording the final levels of FAP and FVP pressures during brief interruptions of CO. FAP and FVP were recorded between the fourth and fifth second after inflation of right atrial balloon (0.05 to 0.3 mL) for 5 seconds. MCFP was calculated using these FAP and FVP values and the VAR. VAR values used in the present study were 76 for the WKY and 106 for the SHR. MCFP was calculated as MCFP=FAP+FVP−(FAP−FVP)/VAR.

Protocol
Conscious rats were placed in loose-fitting Lucite cylinders. These restrainers served only to limit the vertical movements of the rats to reduce movement artifacts in the recording of venous pressure. The rats were trained to the restrainers during the 48-hour surgical recovery period. We have previously shown that use of the restrainers does not affect measurement of MAP or MCFP. The arterial and venous catheters were connected to pressure transducers which led to an A/D system (Biopac Systems) that interfaced with a Macintosh microcomputer (Apple). Blood pressure signals were acquired at 50 Hz and recorded to disk. MAP, HR, and central venous pressure were recorded continuously. MCFP was estimated periodically by inflation of the right atrial balloon. At least 15 minutes was allowed between inflations, which was sufficient for blood pressures and HR to return to preinflation values. Control measurements were taken until MAP, HR, and MCFP remained stable (±5%). The rats were then treated with a subcutaneous injection of chlorisondamine hydrochloride (10 mg/kg) to impair ganglionic transmission. Consistent readings of MAP, HR, and MCFP were obtained after ganglionic blockade. The MAP, HR, and MCFP responses to ganglionic blockade were calculated by subtracting the postganglionic blockade values from the preganglionic blockade values.

Data Analysis
Data are presented as mean±SEM. Absolute values for MAP, HR, and MCFP were analyzed by two-way factorial ANOVA with age and strain as grouping factors. The MAP, HR, and MCFP responses to ganglionic blockade were analyzed with two-way factorial ANOVA using age and strain as grouping factors. Bonferroni’s inequality was used as the post hoc test. Differences were considered significant at a value of P<.05.

Results
MAP, HR, and MCFP at 4 to 6 Weeks of Age
The absolute values for MAP, HR, and MCFP at 4 to 6 weeks of age are illustrated in Fig 1. MAP averaged approximately 91±6 mm Hg in the WKY (n=7), whereas in the SHR in this age group, arterial pressure was 129±6 mm Hg (n=8). HR was 379±21 bpm in the WKY and 418±8 in the SHR. BVP averaged −0.2±0.4 mm Hg in the SHR and −0.1±0.5 mm Hg in the WKY. In contrast, MCFP was significantly increased in SHR at this stage,
averaging 6.6 ± 0.4 mm Hg in the SHR and 5.4 ± 0.4 mm Hg in the WKY. Thus, MAP and MCFP were significantly elevated at 4 to 6 weeks of age in the SHR. HR and BVP were not significantly different between the two groups.

MAP, HR, and MCFP at 8 to 10 Weeks of Age

The absolute values of MAP, HR, and MCFP for SHR and WKY at 8 to 10 weeks of age are illustrated in Fig 2. In this age group, arterial blood pressure was 144 ± 4 mm Hg in the SHR (n = 11) and 102 ± 3 mm Hg in the WKY (n = 7). BVP was not significantly different between SHR (0.4 ± 0.4 mm Hg) and WKY (−0.2 ± 0.2 mm Hg). In contrast, MCFP averaged 7.7 ± 0.3 mm Hg in the hypertensive rats and 6.0 ± 0.2 mm Hg in the control rats. HR was 379 ± 12 bpm and 399 ± 11 bpm in the WKY and SHR, respectively. MAP and MCFP were significantly higher in the SHR, whereas HR and BVP were not different between groups.

ANOVA indicated a significant effect of age on MAP and MCFP but not HR. In SHR, MAP and MCFP were significantly greater in 8- to 10-week-old rats compared with 4- to 6-week-old rats. In contrast, there were no age-related differences in MAP or MCFP in the normotensive WKY rats.

Effects of Autonomic Blockade

To assess the role of the autonomic nervous system in the differences in MAP and MCFP between the SHR and WKY rats, the animals were treated with a ganglion blocking agent, chlorisondamine hydrochloride. In the 4- to 6-week-old rats, administration of chlorisondamine led to a large decrease in MAP, HR, and MCFP in both strains of rat. In the SHR, MAP decreased by 51 ± 6 mm Hg, HR was reduced by 106 ± 19 bpm, and MCFP decreased by 2.7 ± 0.4 mm Hg. In the WKY animals, MAP decreased by 24 ± 4 mm Hg, HR, decreased by 28 ± 15 bpm, and MCFP fell by 1.4 ± 0.2 mm Hg. BVP fell by −0.1 ± 0.2 mm Hg and −0.3 ± 0.1 mm Hg in SHR and WKY rats, respectively. The decreases in MAP, HR, and MCFP were significantly greater in the SHR compared with the WKY rats (Fig 3).

Similarly, ganglionic blockade induced large decreases in MAP, HR, and MCFP in the 8- to 10-week-old rats (Fig 4). In this age group, MAP decreased by 54 ± 6 mm Hg, HR was reduced by 43 ± 14 bpm, BVP decreased by −0.3 ± 0.3 mm Hg, and MCFP fell by 2.7 ± 0.3 mm Hg in the SHR rats. In WKY rats, the MAP, HR, BVP, and MCFP responses to ganglionic blockade were −39 ± 4 mm Hg, −50 ± 16 bpm, −0.6 ± 0.2 mm Hg, and −1.6 ± 0.1 mm Hg, respectively. In this age group, the decrease in MCFP was significantly greater in the SHR compared with the WKY rats.

Autonomic blockade abolished most of the differences in MAP, HR, and MCFP between strains. In SHR of 4 to 6 weeks, MAP, HR, and MCFP averaged 79 ± 7 mm Hg, 312 ± 15 bpm, and 3.9 ± 0.2 mm Hg, respectively, after ganglionic blockade. Postganglionic blockade values for MAP, HR, and MCFP in the 4- to 6-week-old WKY rats averaged 67 ± 5 mm Hg, 351 ± 9 bpm, and 4.0 ± 0.3 mm Hg, respectively. These values were not significantly different statistically. After ganglionic blockade, SHR of 8 to 10 weeks of age had a MAP of 90 ± 5 mm Hg. This value was significantly greater than the corresponding value of 63 ± 3 mm Hg observed in age-matched WKY rats. In contrast, HR (SHR 357 ± 8 versus

Figure 1. Absolute values of MAP, HR, and MCFP in male SHR (n = 8) and normotensive WKY (n = 7) rats at 4 to 6 weeks of age. *Significant differences between strains.

Figure 2. Absolute values of MAP, HR, and MCFP in male SHR (n = 11) and normotensive WKY (n = 7) rats at 8 to 10 weeks of age. *Significant differences between strains.
WKY 329±16 bpm) and MCFP (SHR 5.0±0.3 versus WKY 4.3±0.3 mm Hg) were not different between strains after ganglionic blockade in rats of 8 to 10 weeks of age. As a whole, the results suggest that the elevated MCFP observed in the early stages of spontaneous hypertension is mediated primarily via neurogenic mechanisms.

**Discussion**

A number of studies have suggested that venous function is altered in hypertension. However, the majority of these studies have assessed venous function in the established stages of the disease. Accordingly, it is not clear whether the elevated venous tone observed in hypertensive animals is a compensatory response to hypertension-induced decreases in ventricular compliance.21 The present study was undertaken to test the hypothesis that venous tone is elevated early in the development of spontaneous hypertension. We observed that MCFP, an index of integrated venomotor tone, was significantly elevated in SHR at a very early age. In addition, impairment of autonomic function by ganglionic blockade abolished the elevated venous tone, suggesting that these differences were neurally mediated. Thus, the data obtained in this study indicate that venous function is altered early in the course of development of spontaneous hypertension and may therefore participate in the initiation of the hypertensive process.

A variety of experimental evidence indicates that venous function is altered in hypertensive animals and humans. Mesenteric venules in the SHR are more depolarized than those in age-matched normotensive WKY rats.27 Venous pressure-volume curves are shifted toward the pressure axis in genetic models of hypertension such as the New Zealand hypertensive rat and the SHR,28 indicating a decrease in venous compliance. Similar results have been obtained in human hypertensive subjects.19,21 Direct assessment of the integrated venomotor tone has shown that MCFP is elevated in Goldblatt hypertensive dogs29 and rats.30 Similarly, MCFP is increased in the renal wrap and reduced renal mass models of hypertension18 in the dog and in the SHR model of hypertension.15,16 Thus, it is clear that venous tone is elevated in hypertension. However, because most studies have examined animals in the established phase of hypertension, it is not clear whether the increased venous tone contributes to the development of high blood pressure or represents a compensatory response to maintain filling of a noncompliant heart.

The time course of venous changes associated with the development of hypertension has been examined in a few studies. In the DOCA-salt model of hypertension, MCFP was not elevated after 2 weeks of DOCA treatment but showed a trend to increase by the fifth and eighth week of treatment.31 These results suggest that elevated venous tone is not involved in the developmental stages of this form of hypertension but may play a role in the later stages of the disease. In contrast, rats subjected to one-kidney, one clip Goldblatt hypertension showed an elevation in MCFP after only 3 days of clipping. The elevated MCFP persisted for up to 28 days, suggesting that venoconstriction may be involved in both the initial and maintenance phases of hypertension.30
In the SHR, the most frequently used model of essential hypertension, MCFP is clearly elevated. \(^{15,16}\) However, these studies have been conducted on rats of 16 to 20 weeks of age, which represents the established phase of hypertension. To our knowledge, no previous studies have tested the hypothesis that venous tone is elevated early in the development of spontaneous hypertension. We observed that both MAP and MCFP were significantly elevated in SHR at 4 to 6 weeks of age compared with age-matched normotensive WKY rats. In addition, the differences in arterial pressure and venoconstrictor tone were exaggerated in rats of 8 to 10 weeks of age. Thus, the findings of the present study indicate that integrated venoconstrictor tone is elevated early in the development of spontaneous hypertension.

MCFP was elevated by 1.2 mm Hg at 4 to 6 weeks of age and 1.7 mm Hg at 8 to 10 weeks of age. The magnitude of the venoconstrictor response observed in the present experiments is similar to that reported previously. MCFP was increased by 1.0 mm Hg at 16 weeks of age, \(^{16}\) whereas at 20 weeks of age MCFP was 1.4 mm Hg higher in the SHR compared with age-matched WKY rats. \(^{15}\) Indeed, the degree of venoconstriction reported to occur in hypertension is remarkably consistent across models. In perinephritic hypertensive dogs, MCFP was elevated by 1.5 mm Hg 15 days after renal wrapping, whereas at 10 months the elevation was approximately 1.7 mm Hg. \(^{1}\) In two-kidney, one clip Goldblatt hypertensive rats, MCFP was increased by 1.4 mm Hg compared with the sham-operated controls. \(^{13}\) In one-kidney, one clip hypertensive rats, MCFP was increased by 1.5 mm Hg 3 days after clipping and by 0.8 mm Hg 28 days after clipping. \(^{30}\) Thus, the magnitude of the MCFP elevation observed in the present studies is comparable to that reported previously in several models of hypertension. As a whole, these data suggest that an elevation in venous tone may be a common denominator in the hypertensive process.

In the present study, MCFP was calculated using venous to arterial compliance ratios of 76 and 106 for WKY and SHR, respectively. These values were reported by Samar and Coleman \(^{15}\) for rats of 20 weeks of age. It is possible that these values would be different in younger animals. However, it is unlikely that the use of these previously reported values significantly affected the outcome of these experiments. Samar and Coleman \(^{15}\) have argued convincingly that the correction factor which used the venous to arterial compliance ratio contributes relatively little to the final value of MCFP. Indeed, in the present study, the correction factor contributed approximately 0.2 mm Hg in SHR and 0.2 mm Hg in WKY to the MCFP values calculated for rats at 4 to 6 weeks of age. In the 8- to 10-week-old rats, the correction factor contributed 0.3 mm Hg and 0.3 mm Hg in SHR and WKY rats, respectively. Because these values were not significantly different and are considerably less than the differences in MCFP observed between groups, we feel that it is unlikely that the use of venous to arterial compliance ratios obtained from older rats significantly affected our observations.

It is generally accepted that venous function plays an important role in the control of venous return and CO. The elevated venous tone observed in hypertension may potentially serve two functions. It has been suggested that MCFP may increase in response to decreased cardiac compliance to maintain cardiac filling. \(^{21}\) However, the structural changes associated with ventricular hypertrophy and decreased ventricular compliance are not found in SHR of the age range used in the present studies. \(^{22}\) Alternatively, increased venous tone would increase the driving pressure for venous return and thereby increase CO. CO was not measured in the present study. However, it has been reported that CO is elevated in the early stages of spontaneous hypertension. Smith and Hutchins \(^{4}\) observed that cardiac index was increased by approximately 23% to 33% in the SHR between 35 and 40 days of age compared with age-matched WKY rats. Similarly, Lundin and Nordlander \(^{7}\) found that cardiac index was elevated at an early age in the SHR. In both these studies, TPR was not different between the two strains. Thus, the initial elevation in pressure in the SHR appeared to result from an increase in CO. Previous studies have suggested that elevations in MCFP of 2 to 3 mm Hg could potentially alter CO by up to 40%. \(^{12}\) Recently, in our laboratory, we have observed that interventions that raise MCFP by approximately 1 mm Hg are also associated with an increase in CO of approximately 10% to 15%. \(^{5,6,12}\) Thus, changes in MCFP can have a significant impact on CO. In the present study, we observed a difference in MCFP that ranged from 1.2 to 1.7 mm Hg, which is of sufficient magnitude to have significantly elevated CO. Collectively, these data suggest that this elevated MCFP could have contributed to the higher CO observed in the early stages of spontaneous hypertension. Thus, our findings are consistent with the hypothesis that venoconstriction plays a role in the development of spontaneous hypertension.

The mechanisms responsible for the increase in venous tone observed in hypertension remain controversial. Neural, \(^{7}\) humoral, \(^{33}\) and structural mechanisms \(^{19,28}\) have been advanced to explain the differences in venous tone between hypertensive and normotensive subjects. Relatively few studies have examined the role of the autonomic nervous system in the altered venous function observed in hypertensive subjects. Willems et al. \(^{27}\) found that the difference in resting membrane potential between SHR and WKY rats was abolished by combined α-adrenergic and β-adrenergic blockade, a treatment that also reduced CO in young SHR. \(^{5}\) Prazosin treatment partially reversed the decreased venous compliance observed in human hypertensive subjects. \(^{19}\) In the present study, we assessed the role of neural mechanisms by treating the animals with the ganglionic blocking agent chlorisondamine hydrochloride. In the 4- to 6-week age group the decrease in MCFP was 1.9 times as great (2.7±0.4 versus 1.4±0.2 mm Hg), whereas at 8 to 10 weeks, the decrease in MCFP was 1.7 times that observed in the normotensive rats (2.7±0.3 versus 1.6±0.1 mm Hg). Thus, we found that impairment of autonomic function via ganglionic blockade produced a significantly greater fall in MCFP in the SHR compared with the normotensive WKY rats. Moreover, the absolute values of MCFP were not significantly different between SHR and WKY rats after ganglionic blockade. These findings indicate that, at least in the early stages of spontaneous hypertension, the elevated venoconstrictor tone is mediated primarily via the autonomic nervous system.
Ganglionic blockade with chlorisondamine also markedly affected the differences in MAP between the SHR and WKY rats. In the 4- to 6-week-old rats, MAP was slightly but not significantly elevated in the SHR compared with the WKY after ganglionic blockade. Thus, at this early stage it would seem that the elevated arterial pressures observed in the SHR are maintained primarily via increases in autonomic outflow and/or vascular responsiveness to autonomic effector systems. Moreover, because ganglionic blockade also normalized the differences in MCFP between SHR and WKY rats, this observation is consistent with the possibility that venous tone contributes significantly to the elevated arterial pressure. On the other hand, in 8- to 10-week-old rats, ganglionic blockade reduced but failed to abolish the difference in MAP between the SHR and WKY, despite abolishing the differences in MCFP between the strains. Thus, as hypertension progresses, factors other than autonomic outflow and venous tone are involved in maintaining the elevated arterial pressure.

MCFP is a function of both venous tone and blood volume. It could be argued that the elevated MCFP observed in the young SHR may be due to an increase in circulating blood volume. However, previous studies have found that blood volume is not significantly altered in SHR at this stage of development. Moreover, if blood volume was elevated in the SHR, MCFP should have remained significantly elevated compared with the WKY rats even after autonomic blockade. However, we observed that ganglionic blockade abolished the differences in MCFP between the SHR and WKY rats at both 4 to 6 and 8 to 10 weeks. Accordingly, it seems unlikely that the differences in MCFP were due to differences in circulating blood volumes.

In summary, the present study has demonstrated that MCFP, an index of integrated venomotor tone, is significantly elevated in SHR, at 4 to 6 and 8 to 10 weeks of age compared with age-matched normotensive WKY rats. In addition, the differences in MCFP between groups are abolished by ganglionic blockade. Our findings indicate that venomotor tone increased because of increased autonomic outflow early in the development of spontaneous hypertension. This study supports the hypothesis that veins play an important role in the development of spontaneous hypertension.

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References

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