TOTAL VENOUS CAPACITY IN TWO-KIDNEY, ONE CLIP GOLDBLATT HYPERTENSIVE RATS

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To assess possible time-related changes in total venous capacity, mean circulatory filling pressure (MCFP) and blood volume (BV, Evans blue) were determined in conscious rats with early, intermediate and chronic phases of two-kidney, one clip Goldblatt hypertension. MCFP, an index of whole-body venous activity, was measured while the circulation was arrested by the brief inflation of a balloon inserted into the right atrium. Compared with sham-operated control rats, Goldblatt rats showed unchanged MCFP and BV in early phase, unchanged MCFP with marginally ($0.05 < p < 0.10$) decreased BV in intermediate phase, and significantly ($p < 0.05$) increased MCFP with unchanged BV in chronic phase. Thus, decreased total venous capacity, which is reflected in increased MCFP relative to BV, occurred with a continuation of hypertension. MCFP/BV curves, obtained by measuring MCFP before and after rapid BV change, appeared to shift toward the pressure axis in all Goldblatt groups. There were no significant differences in total vascular compliance, which is the inverse of the slope of this curve and is an index of total venous compliance, between Goldblatt and control groups at any time-period studied. These results suggest that decreased venous capacity observed in chronic hypertensive rats may be a secondary hemodynamic state and may not be related to decreased venous compliance.

THE suggestion has been made that decreased venous capacity or compliance occurs in both clinical^{1,2} and experimental³⁻¹¹ hypertension. Decreased capacity of the venous system, which contains the largest portion of blood, centralizes the blood from the peripheral circulation, thereby changing cardiac filling. Increased cardiac filling in prehypertensive or early phase leads to increased cardiac output, which in turn results in increased peripheral vascular re-

sistance.^{3,4,12-14} Increased cardiac filling in established or advanced phase helps maintain normal cardiac output against increased after-load.^{3,4,12-14}

Mean circulatory filling pressure (MCFP) is a measure of the degree of the filling of the vascular, principally the venous, system with blood, and it is therefore a useful index of the capacity and activity of the venous system.^{15,16} Decreased total venous capacity, which is reflected in increased MCFP with unchanged or contracted blood volume (BV), has been observed in various forms of hypertension, including early Page hypertension in dogs,³ chronic two-kidney, one

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Fig.1. MCFP/BV curves in two-kidney, one clip Goldblatt hypertensive rats 3, 14 or 90 days postclipping. MCFP is mean circulatory filling pressure. Closed circles represent Goldblatt rats and open circles represent control rats. Symbols with bars indicate mean $\pm$ SE. Lines are drawn using average values of data points for purpose of illustration. Group mean compliances are given in Table I.

clip Goldblatt hypertension in rats,⁷ 4- to 5-month-old spontaneously hypertensive rats,^{8,9} early to chronic one-kidney, one clip Goldblatt hypertension in rats,¹⁰ and 3 to 8 days' angiotensin II infusion hypertension in dogs.¹¹ It may be possible that experimental hypertension is associated with decreased venous capacity regardless of its form, its stage, or perhaps its renin status.^{11,17} However, more studies are needed before this notion can be substantiated. The present study was conducted to assess possible time-related alterations in venous capacity during the time from the acute to chronic phase of two-kidney, one clip Goldblatt hypertension (2K, 1C GH) in conscious rats, since a previous observation on this type of hypertension was made only in chronic hypertensive rats using an anesthetic agent which is reported to greatly influence venous capacity.¹⁸

METHODS

Male Wistar rats weighing between 250g and 350 g were used. Under ether anesthesia, a silver clip (slit-size, 0.2 mm) was placed around right renal artery with contralateral kidney left untouched (Goldblatt group), while sham-operation was carried out (control group). All rats were maintained on standard rat chow and tap water *ad libitum*.

Rats were temporarily anesthetized, 3, 14 or 90 days after operation, with ether and then prepared for the experiment.¹⁹ The left femoral artery and vein were cannulated with PE-50

tubing. The femoral arterial line was used for recording arterial pressure. The femoral vein catheter was introduced into the thoracic inferior *vena cava* for recording central venous pressure (CVP). The left carotid artery was cannulated with PE-50 tubing connected to PE-90 tubing for changing BV rapidly. A balloon-tipped catheter was positioned in the right atrium through the right jugular vein. All catheters were brought out at the back of the neck. All wounds were treated with 1% xylocaine during surgery. The rats were allowed 3 hours to recover from surgery and anesthesia. Then each rat was placed in an unconfined box. Pressure readings were determined using Statham transducers and a San-ei polygraph. The pressure baselines were set at the animal's heart level by inspection. The transducer recorder system used was carefully calibrated in a previously described manner.⁹ After 30 min of adaptation, BV, MCFP and MCFP/BV curve were determined.

Plasma volume (PV) was measured with Evans blue. Approximately 0.1 to 0.2 ml of 0.5 w/v % of Evans blue solution was injected into the femoral vein catheter and 5 min later 0.3 ml of blood was taken through the femoral artery catheter. Evans blue concentration was determined spectrophotometrically at 605 m μ . A preliminary study showed no differences in disappearance rate of Evans blue from plasma within this time-period. BV was calculated as follows:

$$BV = PV \div (1 - \text{hematocrit}/100 \times 0.8)$$

TABLE I MEAN CIRCULATORY FILLING PRESSURE, BLOOD VOLUME, AND OTHER VARIABLES IN TWO-KIDNEY, ONE-CLIP GOLDBLATT HYPERTENSIVE RATS 3, 14 OR 90 DAYS AFTER CLIPPING

	3 Days		14 Days		90 Days	
	Goldblatt	Control	Goldblatt	Control	Goldblatt	Control
Number of rats	9	9	9	9	9	9
Body weight (g)	327 ± 3	335 ± 14	303 ± 12	300 ± 12	425 ± 17	447 ± 25
Mean arterial pressure (mmHg)	148 ± 3**	122 ± 2	171 ± 3**	123 ± 2	190 ± 7**	125 ± 3
Central venous pressure (mmHg)	-0.6 ± 0.2	-0.6 ± 0.2	-0.3 ± 0.2	-0.6 ± 0.2	-0.5 ± 0.2	-0.6 ± 0.2
Heart rate (beats/min)	422 ± 9	408 ± 10	418 ± 8	410 ± 6	405 ± 8	423 ± 9
Hematocrit (%)	47.0 ± 0.7	44.6 ± 0.6	43.5 ± 1.2	42.6 ± 0.5	46.8 ± 1.6	47.5 ± 1.2
Plasma volume (ml/kg)	38.6 ± 1.7	42.3 ± 1.4	35.9 ± 1.1	39.0 ± 1.2	34.7 ± 1.0	35.6 ± 1.1
Blood volume (ml/kg)	62.7 ± 2.2	65.2 ± 2.0	55.2 ± 1.4	59.7 ± 1.7	56.3 ± 1.2	57.5 ± 1.9
MCFP (mmHg)	7.7 ± 0.2	7.4 ± 0.2	7.7 ± 0.2	7.1 ± 0.2	8.3 ± 0.2*	7.3 ± 0.2
Total vascular compliance (ml/kg·mmHg)	2.95 ± 0.12	3.06 ± 0.13	2.92 ± 0.14	3.07 ± 0.12	2.93 ± 0.11	3.05 ± 0.11

Values are means ± SE. MCFP = mean circulatory filling pressure, * = $p < 0.05$, ** = $p < 0.01$ in comparison with control groups

where 0.8 is the F-cells factor.¹⁹

MCFP was measured by briefly inflating the balloon and recording arterial pressure and CVP as described elsewhere.¹⁹ While the circulation was arrested with the balloon inflation, CVP increased and reached a plateau within 4 to 5 sec and arterial pressure simultaneously decreased to a lower plateau. The balloon was then quickly deflated and the circulation was restored. MCFP was calculated as follows:

$$\text{MCFP} = \text{VPP} + 1/60 (\text{lowest arterial pressure} - \text{VPP})$$

where VPP is venous plateau pressure, and 1/60 is the ratio of arterial to venous compliance in the rat.¹⁹ To obtain MCFP vs BV relationship, MCFP was also measured immediately after increasing or decreasing BV approximately 6.2 ml/kg (10% of total BV) by rapidly infusing fresh donor blood or withdrawing blood through the right carotid artery^{8,10,19} During this procedure, MCFP was measured 10 sec after the start of the BV change and then BV was restored immediate-

ly. This BV change did not affect steady-state hemodynamic variables. After completion of the BV change procedure, MCFP was measured again at control BV. The baseline MCFP was the average of the 2 control measurements. MCFP/BV curve was obtained for each rat by regression analysis with the method of least squares.^{18,19} Compliance ($\Delta v/\Delta p$) was the inverse of the slope of this curve and represented total vascular compliance^{8,10,18,19}

Statistical analysis was made using Student's *t*-test and level of significance was $p < 0.05$. All values were expressed as means ± SE.

RESULTS

As shown in Table I, mean arterial pressures (MAP) of Goldblatt rats 3, 14, and 90 days post-clipping were 148 ± 3 mmHg, 171 ± 3 mmHg and 190 ± 7 mmHg, respectively, and were significantly higher than those of their corresponding control rats ($p < 0.01$ in all time-periods). Also MAP increased with the passage of time in the Goldblatt groups, while it remained almost the same in the control groups. No significant dif-

ferences were observed in body weight between the Goldblatt and control groups. Hematocrit was not significantly different between the two groups. However, PV and BV tended to be smaller in the Goldblatt group 3 or 14 days post-clipping. In particular, 14 days postclipping, BV was considered to be marginally decreased (55.2 ± 1.4 ml/kg vs 59.7 ± 1.7 ml/kg, $0.05 < p < 0.1$). Compared with the control rats, the Goldblatt rats showed no significant increase in MCFP 3 or 14 days after clipping, whereas they showed significantly increased MCFP (8.3 ± 0.2 mmHg vs 7.3 ± 0.2 mmHg, $p < 0.05$) 90 days after clipping.

As illustrated in Fig. 1, linear regression lines fitted MCFP and BV data points in the MCFP range of 5 to 10 mmHg. Line slopes reflected the mean values of total vascular compliance obtained for each group. The MCFP/BV relationship appeared to shift toward the MCFP axis in a parallel fashion in all Goldblatt groups. As indicated in Table I, comparison of the group mean of total vascular compliance showed no significant differences between the Goldblatt and control groups at any time-period studied. There were also no differences in CVP or heart rate between the two groups.

DISCUSSION

Average MCFP observed in Japanese Wistar rats of control groups ranged from 7.1 mmHg to 7.4 mmHg. The value in normal American Wistar rats was 7.6 mmHg¹⁸ or 7.9 mmHg¹⁹, and that in Wistar Kyoto rats from American colonies was 7.7 mmHg¹⁸ or 8.0 mmHg¹⁹. Thus, MCFP appeared to vary only slightly in rats, although it varied considerably in dogs.^{11,15,21}

Significant increase in MCFP with unchanged BV in 2K, 1C GH rats 90 days postclipping was the positive finding in the present study. It might be argued that increase in MCFP by 1 mmHg is too small to have a scientific meaning, or is not enough to exert a significant effect on BV centralization. However, it is pointed out that careful setting of the sensitivity and resolution of the transducer recorder system enabled us to deal with such a change.⁹ Moreover, according to Guyton's cardiac output and venous return curves,¹⁶ if other basic circulatory parameters remain unchanged, a 1 mmHg increase in MCFP can increase cardiac output by as high as 20%. Also unchanged MCFP with a decreased BV, even if statistically insignificant ($0.05 < p < 0.1$), in 2K, 1C GH rats at 14 days postclipping

must be taken into consideration. Therefore, the present findings were interpreted as indicating that total venous capacity was unchanged in the early phase, marginally decreased in the intermediate phase, and significantly decreased in the chronic phase in 2K, 1C GH rats. The result in the chronic hypertensive rats supports the previous work which demonstrated increased MCFP and reduced BV in anesthetized rats with this form of hypertension 9 weeks after clipping.⁷ With regard to BV, somewhat smaller BV observed herein was not inconsistent with previous reports.^{7,23}

Unchanged venous capacity observed in the early phase suggests that venous alteration is not always associated with all phases of hypertension. The present results imply that venous alteration is a time-dependent hemodynamic consequence of sustained hypertension. The cardiovascular system adapts to a long-standing increase in peripheral vascular resistance on one hand by increasing cardiac muscle size, and on the other hand by decreasing blood-holding vascular capacity, whereby facilitating cardiac filling increase without necessity of BV expansion, and adaptation helps maintain normal cardiac output. Consistent with this implication is an observation on normal baseline cardiac output, significant cardiac hypertrophy, and moderate (although statistically insignificant) elevation of left ventricular end-diastolic pressure in rats with 2K, 1C GH of 6 to 22 weeks' duration.²³ The present findings contrasted with those of the previous study showing early (3 days postclipping) decrease in venous capacity in one-kidney, one clip Goldblatt hypertensive (1K, 1C GH) rats.¹⁰ The difference may be attributable to the speed of the development of hypertension: hypertension developed gradually in the present 2K, 1C GH experiment, while more acutely in the previous 1K, 1C GH experiment.¹⁰ Rapidly developing hypertension may require rapid venous change. However, the possibility must not be dismissed that although late venous change is a secondary hemodynamic state in 2K, 1C GH rats, early venous change may be a primary factor in 1K, 1C, GH rats. It is suggested that reduced venous capacity or compliance, with or without BV expansion, contributes to an early increase in cardiac output, and therefore, plays an important role in the initiation of some experimental hypertension.^{3,4,12-14}

A nearly parallel leftward shift of the MCFP/BV curve in the Goldblatt groups implies no

difference in line slopes (Fig. 1). This finding was quantitatively substantiated by obtaining no differences in total vascular compliance between the Goldblatt and control groups (Table I). Total vascular compliance is regarded here as an index of total venous compliance, since the arterial to venous compliance ratio is very low in the rat^{8,19}. Therefore, these results suggest no change in total venous compliance in the Goldblatt rats. Hence, it appears that decreased venous capacity in chronic 2K, 1C GH rats is related to changes in unstressed vascular volume (BV at MCFP = 0).^{11, 18,19} These findings were in agreement with results of spontaneously hypertensive rats,⁸ while they were in contrast with observation of decreased venous compliance in 1K, 1C GH rats.¹⁰ Total vascular compliance, estimated from MCFP/BV curves, is influenced by reflex veno-activity changes during rapid BV alterations.^{19,21} Therefore, these different results may possibly come from different reflex responses among hypertensive rats, although no supporting data are available. Yet, the differences may reflect real differences in venous alterations related to basic mechanisms underlying each hypertension, although the precise implication is unclear.

This study offered no information regarding mechanisms of the venous alteration. Possible factors to be considered are increased venous tone due to increased sympathetic activity,¹⁴ enhanced responsiveness of veins to sympathetic stimuli,^{14,24} decreased interstitial tissue compliance,^{4-6,9,25} and structural venous changes due to "water lodging",⁴⁻⁶ wall composition change^{4-6,26} or unknown humoral substance.²⁷ Although prolonged angiotensin II infusion reduced total venous capacity in dogs,¹¹ angiotensin II may not be a responsible factor in our Goldblatt rats; the hypertensive rats 3 days post-clipping with perhaps the highest activation of the renin-angiotensin system exhibited no change in venous capacity. No increase in circulating noradrenaline was observed in this form of hypertension,²⁸ although sympathetic activity may vary, depending on stages of hypertension or occurrence of cardiovascular complications. Tissue compliance alterations were recently eliminated in case of spontaneously hypertensive rats,⁹ but they were not studied yet in this form of hypertension. Thus, there is no conclusive evidence accounting for mechanisms of venous changes.

REFERENCES

1. WALSH JA, HYMAN C, MARON de RF: Venous distensibility in essential hypertension. *Cardiovasc Res* 3: 338, 1969
2. LONDON GM, SAFAR ME, SIMON AC, ALEXANDRE JM, LEVENSON JA, WEISS YA: Total effective compliance, cardiac output and fluid volumes in essential hypertension. *Circulation* 57: 995, 1978
3. FERRARIO CM, PAGE IH, McCUBBIN JW: Increased cardiac output as a contributory factor in experimental renal hypertension in dogs. *Circ Res* 27: 799, 1970
4. OVERBECK HW: Hemodynamics of early experimental renal hypertension in dogs: Normal limb blood flow, elevated limb vascular resistance and decreased venous compliance. *Circ Res* 31: 653, 1972
5. SIMON G, PAMNANI MB, DUNKEL JR, OVERBECK HW: Mesenteric hemodynamics in early experimental renal hypertension in dogs. *Circ Res* 36: 791, 1975
6. SIMON G: Altered venous function in hypertensive rats. *Circ Res* 38: 412, 1976
7. GOTZEN R, HERBERG C, SCHULTZE G, LOHMANN FW: Statischer Druck, Blutvolumen und zentralvenöser Druck bei renovaskularer Hypertonie. *Archiv Kreislaufforschg* 66: 66, 1971
8. SAMAR RE, COLEMAN TG: Mean circulatory filling pressure and vascular compliances in the spontaneously hypertensive rat. *Am J Physiol* 237: H584, 1979
9. TRIPPODO NC, YAMAMOTO J, FROHLICH ED: Whole-body venous capacity and effective total tissue compliance in SHR. *Hypertension* 3: 104, 1981
10. YAMAMOTO J, TRIPPODO NC, MacPHEE AA, FROHLICH ED: Decreased total venous capacity in Goldblatt hypertensive rats. *Am J Physiol* 240: H487, 1981
11. YOUNG DB, MURRAY HR, BENGIS RG, MARKOV AK: Experimental angiotensin II hypertension. *Am J Physiol* 239: H391, 1980
12. LEDINGHAM JM, PELLING D: Cardiac output and peripheral resistance in experimental renal hypertension. *Circ Res* 20, 21 (Suppl II): 187, 1967
13. COLEMAN TG, GRANGER HJ, GUYTON AC: Whole-body autoregulation and hypertension. *Circ Res* 28 (Suppl II): 76, 1971
14. FERRARIO CM, PAGE IH: Current views concerning cardiac output in the genesis of experimental hypertension. *Circ Res* 43: 821, 1978
15. GUYTON AC, POLIZO D, ARMSTRONG GG: Mean circulatory filling pressure measured immediately after cessation of heart pumping. *Am J Physiol* 179: 261, 1954
16. GUYTON AC, JONES CE, COLEMAN TG: Circulatory Physiology: Cardiac Output and Its Regulation. Philadelphia, Saunders, 1973
17. YAMAMOTO J: Role of the renin-angiotensin system in experimental hypertension in rats: Plasma renin and hypotensive effect of angiotensin II antagonist. *Jpn Circul J* 41: 665, 1977
18. SAMAR RE, COLEMAN TG: Measurement of

- mean circulatory filling pressure and vascular capacitance in the rat. *Am J Physiol* 234: H94, 1978
19. YAMAMOTO J, TRIPPODO NC, ISHISE S, FROHLICH ED: Total vascular pressure-volume relationship in the rat. *Am J Physiol* 238: H823, 1980
 20. WANG L: Plasma volume, cell volume, total blood volume and F-cells factor in the normal and splenectomized Sherman rats. *Am J Physiol* 196: 188, 1958
 21. DREES JA, ROTHE CF: Reflex venoconstriction and capacity vessel pressure-volume relationships in dogs. *Circ Res* 34: 360, 1974
 22. KURIHARA H, TANAKA T, TERASAWA F, SAEKI M, IKEDA M: Difference in changes of plasma volume in two types of Goldblatt hypertension in rabbits. *Tohoku J Exp. Med* 118: 113, 1976
 23. AVERILL DB, FERRARIO CM, TARAIZI RC, SEN S, BAJBUS R: Cardiac performance in rats with renal hypertension. *Circ Res* 38: 280, 1976
 24. BEVAN JA, BEVAN RO, PEGRAM BL, PURDY RE, SU C: Increased responsiveness of veins to adrenergic stimulation in experimental hypertension. *Blood Vessels* 11: 241, 1974
 25. LUCAS J, FLOYER MA: Changes in body fluid distribution and interstitial tissue compliance during the development and reversal of experimental renal hypertension in the rat. *Clin Sci Mol Med* 47: 1, 1974
 26. PAMNANI MB, OVERBECK HW: Abnormal ion and water composition of veins and normotensive arteries in coarctation hypertension in rats. *Circ Res* 38: 375, 1976
 27. SIMON G: Venous changes in renal hypertensive rats: The role of humoral factors. *Blood Vessels* 15: 311, 1978
 28. DARGIE HJ, FRANKLIN SS, REID JL: Central and peripheral noradrenaline in the two kidney model of renovascular hypertension in the rat. *Br J Pharmacol* 61: 213, 1977