PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 152, 122-125 (1976)

Decreased Venous Compliance in Dogs with Chronic Renal Hypertension[1] (39341)

GEZA SIMON, MOTILAL B. PAMNANI, AND HENRY W. OVERBECK

Department of Physiology, Michigan State University, East Lansing, Michigan 48824

In essential hypertensive patients, evidence for decreased digital and forearm venous compliance was found by plethysmography (1, 2). In spontaneously hypertensive rats, Greenberg and Bohr (3) reported decreased passive extensibility of portal vein strips. In earlier studies, we found decreased compliance of femoral (4) and mesenteric veins (5) in dogs with early one-kidney perinephritic hypertension. The purpose of the present study was to extend our previous investigations by determining whether the decreases in venous compliance persist into the chronic (more than 4 weeks) stage of one-kidney perinephritic hypertension in dogs. We observed pressure-volume relationships in isolated segments of femoral veins. We also examined the veins histologically, and measured their water and electrolyte contents in an attempt to define the mechanisms responsible for the decreases in venous compliance in hypertension.

Materials and methods. Twenty-seven healthy, male mongrel dogs, weighing 19-29 kg, were trained to lie quietly during femoral arterial punctures for weekly blood pressure measurements. Mean arterial blood pressure less than 130 mm Hg was documented in each dog prior to surgery. During the entire study period the dogs were maintained on standard dog chow (Wayne Dog Food) and water *ad libitum*. In fourteen dogs, randomly selected, one kidney was wrapped in silk and the other kidney was removed 1 week later (experimental group). Thirteen other dogs underwent sham-wrapping and contralateral nephrectomy at similar time intervals (control group). Operative procedures were similar to those we have previously described (5). Four to 24 weeks following nephrectomy, the dogs, fasted 24 hr, were anesthetized with sodium thiamylal (13.2 mg/kg iv) and mechanically ventilated. Blood was obtained for hematocrit, serum creatinine (autoanalyzer), and serum sodium and potassium (flame photometer) measurements. A 5-cm segment of femoral vein (FV), downstream from the branching of the caudal FV, was dissected *in situ*. With collaterals tied off and cut near their origins, the FV segment was removed and transferred to a chamber containing Krebs-Ringer (K-R) bicarbonate solution (NaCl, 118.3 m*M*; KCl, 4.7 m*M*; $MgSO_4$, 1.2 m*M*; KH_2PO_4, 1.2 m*M*; $CaCl_2$, 2.5 m*M*; $NaHCO_3$, 25.0 m*M*; and glucose, 11.1 m*M*) kept at 37° and aerated with 95% O_2 and 5% CO_2 gas mixture (Fig. 1). The pH of the solution was adjusted to 7.40-7.43 with 0.1 *N* HCl. After tying each end of the cut venous segment to a thin-walled glass cannula, the *in vitro* length of the vein was adjusted to 4 cm. The vein was perfused at 25 ml/min with the same K-R solution used in the chamber. To measure venous pressure-volume relationships, perfusion was stopped, the inflow and outflow tubes were clamped, and intraluminal pressure was adjusted to atmospheric pressure. The system was checked for fluid leakage by injecting K-R solution until an intraluminal pressure of 40-50 mm Hg was reached and then by retrieving all injected solution. Thereafter, FV pressure-volume relationships were obtained by rapid continuous infusion at 3.88 ml/min (Harvard infusion-withdrawal pump), reaching 40-50 mm Hg intraluminal pressure maximum in 5-15 sec. These measurements were repeated at least twice at 25-min intervals. At the end of the experiment, the venous segment was weighed to within ±0.001 g.

Using the average of two or three pressure-volume measurements, a venous pressure-volume curve was constructed for each dog. Volumes (milliliters) producing intra-

[1] This work was supported by U.S. Public Service Grant No. HL-15146 from the National Heart and Lung Institute, and by a research grant from the Michigan Heart Association.

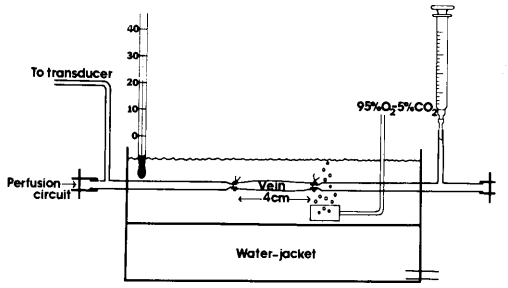

FIG. 1. Schematic drawing of apparatus used to study venous pressure-volume relationships *in vitro*.

luminal pressures of 5, 15, 25, and 35 mm Hg in hypertensive dogs were compared to corresponding values in normotensive control dogs by Student's t test. Similarly, pressures (mm Hg) reached after the infusion of 0.13, 0.26, 0.39, and 0.52 ml of fluid and calculated compliances ($\Delta V/\Delta P$) in the pressure range of 0–15 mm Hg in hypertensive dogs were compared to corresponding values in normotensive control dogs. The data were also analyzed by profile analysis (6). This latter analysis takes into consideration the fact that the data points were not independent, thereby inducing correlation of errors. In this latter analysis, we tested the null hypotheses that the pressure-volume curves of hypertensives and normotensives, over the volume range of 0–0.52 ml, were parallel and not displaced from one another. For these analyses, several pressures in the higher volume ranges were derived by extrapolation from the individual pressure-volume curves. Null hypotheses were rejected at $P \leq 0.05$.

During the dissection of the FV, an additional segment of the vein was removed for analysis of water, sodium, and potassium contents. Water content was measured by weighing before and after oven-drying the vein at 100° for 24 hr. The sodium and potassium contents were determined with a Beckman Model 105 Flame Photometer, following digestion of venous tissue with 0.1 N HNO_3 for 2 weeks. The water content, milliliters per kilogram wet weight, and sodium and potassium contents, milliequivalents per kilogram dry weight, of veins from hypertensive dogs were compared with corresponding values of control dogs by Student's t test, rejecting null hypotheses at $P \leq 0.05$.

Finally, in three hypertensive and three control dogs, a segment of the contralateral FV was removed for histological examination. Serial sections of veins were stained with hematoxylin and eosin, Wilder's reticulin, Verhoff's elastica, Gomori's trichome, Lillie's allochrome, and AB PAS stains.

Results. Initially, mean arterial blood pressure (MABP) in the experimental group was 113 mm Hg ($N = 14$). After one kidney was wrapped in silk and the opposite kidney removed, MABP in unanesthetized dogs rose to 170 mm Hg ($P < 0.001, N = 14$) at the time of the venous pressure-volume studies. The average time from the induction of perinephritis to the time of the pressure-volume studies was 66 days ($N = 14$). The average duration of hypertension (statistically significant increase in MABP) was 44 days ($N = 13$). Hypertension was present in all dogs for at least 4 weeks. Initially, MABP in the control group was 109 mm Hg, and there was no significant change ($P > 0.5, N = 13$) in MABP following sham surgery and contralateral nephrectomy. At the time of the hemodynamic studies, the mean body weights of hypertensive and of control dogs, 25.8 and 25.5 kg, were not significantly different ($P > 0.5$). The general health of all dogs remained good. The venous blood hematocrit (volume percent) of hypertensive and normotensive dogs at the time of the hemodynamic studies was within normal limits. The serum creatinine and serum concentrations of sodium and potassium in hypertensive ($N = 7$) and control normotensive ($N = 7$) animals were also within normal limits and not significantly different ($P > 0.5$). The mean weight of the femoral vein (FV) segments from hypertensive dogs used for pressure-volume studies (0.125 g) did not significantly differ ($P > 0.1$) from that of control dogs (0.137 g).

In hypertensive dogs, the volumes infused to reach 15, 25, and 35 mm Hg were significantly less ($P < 0.05$) (Fig. 2) and the intraluminal pressures reached after the infusion of 0.39 and 0.52 ml of fluid were significantly greater ($P < 0.05$) (Table I) than in normotensive dogs. In the pressure range of 0–15 mm Hg, the calculated femoral vein compliance of hypertensive dogs was significantly reduced compared to that

of normotensive dogs ($P < 0.05$) (Table I). The pressure-volume curves of both hypertensive and normotensive dogs were convex toward the volume axis. There was a statistically significant shift of the pressure-volume curves of hypertensive dogs toward the pressure axis (Fig. 2). This displacement of the pressure-volume curve in hypertensive dogs was confirmed by profile analysis ($P < 0.05$); this analysis, however, indicated that the two curves were parallel ($P > 0.2$), i.e., their shapes were similar.

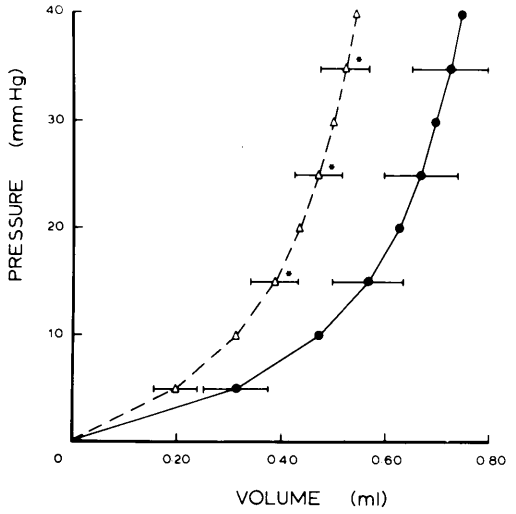

FIG. 2. *In vitro* femoral vein pressure-volume curves, means of groups. Solid and interrupted lines indicate the pressure-volume curve of control ($N = 13$) and hypertensive ($N = 14$) dogs, respectively. Horizontal bars represent ±SEM; * $P < 0.05$.

TABLE I. *IN VITRO* FEMORAL VEIN PRESSURE-VOLUME RELATIONSHIPS AND COMPLIANCES.[a]

	Control ($N = 13$)	Hypertensive ($N = 14$)
	Pressure (mm Hg)	
Volume (ml)		
0.13	3.3 ± 0.6	5.2 ± 0.9
0.26	6.5 ± 1.3	13.0 ± 2.9
0.39	11.0 ± 2.9	27.0 ± 6.8*
0.52	20.0 ± 5.1	46.0 ± 10.4*
	Compliance, $\Delta V/\Delta P$ (ml/mm Hg)	
Pressure range (mm Hg)		
0–15	0.0376 ± 0.0045	0.0256 ± 0.0031*

[a] Results are expressed as group means ± SE.
* $P < 0.05$, for comparisons between hypertensive and control groups.

The water and sodium contents of the femoral veins from hypertensive dogs were significantly greater than those of veins from control dogs (Table II).

Histological examination of the stained sections of the femoral veins provided no evidence for venous wall abnormalities in hypertensive dogs. Specifically, there was no evidence for smooth muscle hypertrophy or proliferation, increased adventitial collagen, reticulin or fibrous fibers, accumulation of neutral or acid mucopolysaccharides, and endothelial cell hyperplasia and/or swelling.

Discussion. In a previous study, Overbeck (4) observed that the pressure-volume curve of the femoral vein (FV) of dogs with early (less than 4 weeks) one-kidney, perinephritic hypertension is shifted in the direction of the pressure axis, direct evidence that venous compliance may be decreased. In a subsequent study (5), we found that the mesenteric vein pressure-volume curve in early one-kidney perinephritic hypertensive dogs is also shifted toward the pressure axis. This was true both in *in vivo* and in *in vitro* studies. Active venoconstriction did not seem to be responsible for this decreased venous compliance because the pressure-volume curves in both hypertensive and normotensive dogs were convex toward the volume axis; venoconstriction characteristically changes the pressure-volume curve to a sigmoid configuration (7). Furthermore, in hypertensive dogs sodium cyanide, which abolishes smooth muscle tone, did not change the shape of the pressure-volume

TABLE II. VENOUS WALL WATER, SODIUM, AND POTASSIUM CONTENT IN CONTROL AND HYPERTENSIVE DOGS.[a]

	Control	Hypertensive
Water (ml/kg wet weight)	633 ± 17 $N = 10$	684 ± 11* $N = 10$
Sodium (mEq/kg dry weight)	277.6 ± 21.6 $N = 8$	353.1 ± 21.7* $N = 8$
Potassium (mEq/kg dry weight)	68.7 ± 12.7 $N = 9$	75.6 ± 24.6 $N = 9$

[a] Results are expressed as group means ± SE.
* $P < 0.05$, for comparison between hypertensive and control group.

curves or prevent the shift toward the pressure axis. Subsequently, Pamnani and Overbeck (8) reported increased water, sodium, and potassium contents of veins in one-kidney Goldblatt hypertensive rats, an observation that might account for the changes that we had observed in venous compliance.

The findings of our present study extend these previous observations to dogs with chronic perinephritic hypertension. Again, in these chronic renal hypertensive dogs, the FV pressure-volume curves are shifted toward the pressure axis, suggesting decreased venous compliance. Again, the convexity of the pressure-volume curves is towards the volume axis, suggesting that the mechanism responsible for the decreased venous compliance does not involve active venoconstriction. By light microscopy we could not demonstrate histological changes, but we did find increased water and sodium contents of these same veins. Therefore, we suggest that venous wall "edema" may account for the decreases in venous compliance. It has similarly been suggested that the decreased arterial compliance in dogs with renal hypertension may be attributable to increased water content of arterial walls (9).

Regarding the pathogenesis of decreased compliance, our *in vitro* studies effectively eliminate the possibility that humoral and neural factors were immediately responsible for the observed changes. However, it is possible that the decreased compliance and the abnormal composition of the FV could have been the residual effects of humoral or neural factors.

Ferrario *et al.* (10) found increased cardiac output in early one-kidney perinephritic hypertensive dogs. In the chronic stage of hypertension, cardiac output returned to normal. Their dogs were prepared similarly to ours. The decreased femoral and mesenteric vein compliance that we found in early hypertension may contribute to the initial rise of cardiac output by increasing venous return. However, the present study indicates that this reduction of femoral vein compliance apparently persists into the chronic stage of hypertension. If veins throughout the body are similarly affected, then the present findings suggest that the return to normal of cardiac output in the chronic stage of hypertension is due to mechanisms other than the return of venous compliance to normal.

Summary. Femoral vein (FV) pressure-volume relationships were measured *in vitro* in 14 dogs with chronic (more than 4 weeks), one-kidney perinephritic hypertension and in 13 unilaterally nephrectomized normotensive control dogs. Segments of FV were also examined histologically and analyzed for their water and electrolyte contents. Compared to controls: (i) the FV pressure-volume curves of hypertensive dogs were shifted toward the pressure axis ($P < 0.05$); (ii) calculated venous compliance in the pressure range of 0–15 mm Hg was decreased ($P < 0.05$); and (iii) the water and sodium contents of veins from hypertensive dogs were increased ($P < 0.05$). Histological examination of the FV from hypertensive and control dogs did not reveal significant differences. The findings indicate that the decreases in venous compliance that we have previously observed in the early stages (less than 4 weeks) of perinephritic hypertension in dogs persist into the chronic stage of hypertension. Venous wall "edema" may account for the decreased venous compliance in this form of hypertension.

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Received July 14, 1975. P.S.E.B.M. 1976, Vol. 152.