Hypertension caused by salt loading. 
II: Fluid volume and tissue pressure changes

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Experimental hypertension was produced in dogs by increasing their dietary intake of sodium chloride after removing approximately 70% of their renal tissue. The changes in mean arterial pressure, interstitial fluid pressure, blood volume, and sodium space were observed during the development and maintenance of the hypertension. During the periods of increased salt intake, the arterial pressure increased from a mean of 114.6 mm Hg to a mean of 150.6 mm Hg, and there were concomitant increases of 19.8% in blood volume, 16% in sodium space, and 4 cm H2O in interstitial fluid pressure. However, the increases in all the parameters studied except arterial pressure were transient. The blood volume remained elevated above control values for a longer period of time than the sodium space and interstitial fluid pressure, but it reapproached normal after approximately 16-20 days.

Several workers have investigated the possibility that an increase in blood volume or extracellular fluid volume might be involved in the development of experimental renal hypertension. Griffith and Ingle found a concomitant increase in blood volume when arterial pressure was elevated in rats as a result of salt loading after partial nephrectomy (5). On the other hand, studies reported by others (1, 11) have failed to demonstrate increased blood volume under similar conditions in dogs and rats. Experiments reported by still other investigators have indicated that at least some types of experimental hypertension are accompanied by an elevation of extracellular fluid volume (7, 9, 10). Houck concluded from his experiments that a hydrated state is necessary for development of hypertension but is not necessary for maintenance of hypertension (7).

The experiments to be reported here were designed to follow changes in blood volume and sodium space at all stages of the development and maintenance of hypertension in salt-loaded, partially nephrectomized dogs. Also, a newly reported method for measuring interstitial fluid pressure (6) has been used to study the changes in this pressure concomitant with the changes in fluid volume. These parameters have been correlated with the change in arterial pressure.

**METHODS**

Twelve medium-sized, mongrel dogs were subjected to alternate periods of normotension and hypertension in this study. The methods used to alter arterial pressure have been described in a previous report from this laboratory which showed that an increased intake of sodium chloride would produce hypertension in partially nephrectomized dogs (8). The blood volume and the sodium space were determined in eight of the animals which drank tap water during the establishment of control values and were then required to drink 0.9% saline for an additional 2 weeks. The blood volume and tissue pressure were determined in four of the animals that drank tap water while controls were established and then were required to drink 1.2% saline for 5 weeks, after which they were again allowed to drink tap water.

The blood volume was measured by the dilution technique using Evans blue dye (T-184). The Na24 space was determined by using the standard dilution principle and the technique described by Beierwaltes et al. (2). The method described by Guyton was used to determine the interstitial fluid pressure (6).

The blood volume and interstitial fluid pressure were determined each time the arterial pressure was measured, approximately three times each week. The sodium space was measured once each week throughout the study.
Changes in arterial pressure, blood volume, and tissue pressure before, during, and after a period of increased salt intake in partially nephrectomized dogs. Standard errors of the mean are indicated.

FIG. 1. Changes in arterial pressure, blood volume, and tissue pressure before, during, and after a period of increased salt intake in partially nephrectomized dogs. Standard errors of the mean are indicated.

FIG. 2. Changes in mean arterial pressure and sodium space in partially nephrectomized dogs resulting from changes in salt intake.

RESULTS

Effect of salt-loading hypertension on blood volume. Figure 1 shows the effect of salt loading on arterial pressure, blood volume, and tissue pressure in partially nephrectomized dogs. These are average results obtained from four dogs with approximately 70% of their renal tissue removed. Arterial pressure rose to hypertensive levels (38.5 ± 2.0 SEM above control) within 1 week after 1.2% saline was substituted for the dog's drinking water, and the pressure remained elevated throughout the 35-day period of drinking 1.2% saline.

The average control blood volume for all four dogs during the 8 weeks prior to sodium loading was 81.8 (±1.9 SEM) ml/kg. The partial nephrectomy had no measurable effect on the blood volume, but there was an average increase of 17.5% (±2.8 SEM) during the first 14 days after the animals began to drink the 1.2% saline solution. This increase in volume was statistically highly significant with a P value of less than 0.001. However, the blood volumes returned to a level only slightly greater than the control value (difference not statistically significant) by 20 days and remained there even though the arterial pressure remained at hypertensive levels.

Blood volumes were also measured in eight additional dogs which drank 0.9% saline for 2 weeks, tap water for 2 weeks, and 0.9% saline for an additional 2 weeks. There was an average increase of 21% (±2.6 SEM) in blood volume and an average increase in arterial pressure of 37 (±4.4 SEM) mm Hg in this group of animals during the 2-week period of drinking the saline solution; however, they returned to control levels within 1 week after the animals were again allowed to drink tap water.

Changes in interstitial fluid pressure during development of salt-loading hypertension. Control interstitial fluid pressures were established in the animals studied in Fig. 1 prior to substituting 1.2% saline for drinking water. The control pressures were always in the negative range, averaging -6.4 (±0.8 SEM) cm H2O. During the development of hypertension, however, the pressure rose to an average maximum of -2.4 (±0.4 SEM) cm H2O as shown in Fig. 1. This rise was statistically significant with a P value of less than 0.01; however, it was transient and returned to control levels within 7-14 days. The interstitial fluid pressure then remained at the control level throughout the remainder of the hypertensive phase.

Effect of salt-loading hypertension on sodium space. The sodium space and arterial pressure were studied in eight dogs that drank 0.9% saline. Figure 2 shows the results from the entire group of dogs. The arterial pressure rose an average of 37 (±4.4 SEM) mm Hg when the dogs drank saline. The sodium space increased an average of 16 ± 2.4% (P less than 0.001) during the development phase of the hypertension, but this was a transient increase. Within 14 days the sodium space had returned to a level slightly below the control level (not statistically significant) although the animals were still hypertensive. At the end of the 14-day period of drinking saline the animals were allowed to drink tap water, and although the arterial pressures returned to normotensive levels, there was no significant change in sodium space. This transient increase in sodium space occurred a second time in each dog when 0.9% saline was substituted once again for drinking water for a period of 14 days.

DISCUSSION

The experiments presented in this report have confirmed our previous findings that dogs with 70% of their renal mass removed will develop severe hypertension within 2-3 days when their intake of sodium chloride is
increased sufficiently, and that this hypertension disappears when the increased salt intake is reduced to normal.

One is strikingly impressed by the fact that the Na\textsuperscript{+} space, the blood volume, and the interstitial fluid pressure were all elevated while the arterial pressure was rising, almost as if the volume and tissue pressure changes played a role in the development of the hypertension.

Borst (3) has postulated that extracellular and blood volume increases can contribute to the development of hypertension. And Conway (4) has demonstrated that maintenance of increased blood volume for many hours by means of continuous infusion causes the cardiac output and arterial pressure to increase the first hour or so, followed within another few hours by return of the cardiac output to normal. He has shown that hypertension persists because of a progressive increase in total peripheral resistance though the cardiac output has returned to normal. In this instance, the entire sequence of events was initiated by a simple increase in volume.

Whether this sequence of events takes place during the development of hypertension in partially nephrectomized, salt-loaded dogs, or whether these fluid volume changes are only incidental or secondary effects still remains to be resolved.

Regardless of whether the changes in fluid volumes play a role in the development and maintenance of this type of hypertension, these findings suggest an answer to the fact that some investigators have reported that the fluid volumes are increased in certain types of experimental hypertension while others have been unable to confirm these results.

REFERENCES