Hypertension Caused by Salt Loading in the Dog

III. ONSET TRANSIENTS OF CARDIAC OUTPUT AND OTHER CIRCULATORY VARIABLES

By **Thomas G. Coleman, Ph.D., and Arthur C. Guyton, M.D.**

ABSTRACT

Experimental hypertension was produced in dogs by salt loading after renal mass had been surgically reduced to an estimated one-third normal. Salt loading was accomplished in one group of five dogs by administering isotonic saline in lieu of drinking water and in another group of six dogs by continuously infusing isotonic saline. Arterial pressure, cardiac output, heart rate, stroke volume, and total peripheral resistance were determined at frequent intervals during a 1-week control period and a 2-week salt-loading period in both groups. In addition, right atrial pressure, blood urea nitrogen, serum sodium, and serum potassium were determined in the group that was continuously infused. Both groups demonstrated an increase in mean arterial pressure to hypertensive levels, transiently increased cardiac output and stroke volume, initially depressed then subsequently increased total peripheral resistance, and initially depressed and variable heart rate. It is concluded that salt loading in a partially nephrectomized dog causes elevated arterial pressure that is initially induced by increased cardiac output but that is eventually sustained by increased peripheral resistance. Possible mechanisms are discussed.

ADDITIONAL KEY WORDS arterial pressure partial nephrectomy peripheral resistance

■ Though hypertension theoretically could be caused by an increase in either total peripheral resistance or cardiac output, only occasionally is elevated cardiac output implicated as a cause of chronically increased blood pressure. Once an animal or a human being has reached an equilibrated hypertensive pressure, his total peripheral resistance almost invariably is elevated as much as the pressure itself, for which reason the statement is often made that the basic cause of most types of hypertension is increased peripheral resistance.

Yet, during the past dozen years a theory has developed for the causation of hypertension based on an initial rise in cardiac output followed secondarily by a rise in total peripheral resistance. This theory has been referred to by different names but may be called the "autoregulation" theory. Theoretically, some factor, such as increased fluid volumes or some other change in the circulation, causes an initial increase in cardiac output. This increase results in excess blood flow through the tissues which in turn supposedly initiates an autoregulatory response that causes arteriolar constriction. The constriction increases the total peripheral resistance and at the same time decreases the cardiac output back toward normal. Fries (1) and Borst (2) have amassed considerable clinical evidence which they believe supports this concept. Also, experimental studies from Ledingham's laboratory (3) have indicated that the cardiac output rises in Goldblatt rats with the onset of hypertension and that this

From the Department of Physiology and Biophysics, University of Mississippi School of Medicine, Jackson, Mississippi 39216.

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perhaps causes the total peripheral resistance to increase secondarily. On the other hand, Olmsted and Page (4), in studying Goldblatt dogs, found a decrease in cardiac output during the onset of hypertension which seemed to refute the autoregulation concept of hypertension. Yet, both Ledingham and Olmsted found it extremely difficult to maintain controlled conditions in their animals throughout the period of study, particularly in the face of the operation that was necessary to establish the Goldblatt preparation.

An alternative experimental model in which the autoregulation concept can be tested consists of reducing renal mass in the dog to approximately 30% of normal and then increasing salt and water intake. The increase in salt and water intake and, consequently, the onset of hypertension are initiated 10 days to 2 weeks following completion of surgery, and in this way the possibility that the trauma of surgery will inadvertently bias the data is avoided.

Previously Koletsky and Goodsitt (5, 6) demonstrated that a combination of subtotal nephrectomy and increased salt intake is necessary consistently to produce hypertension in rats. In studies with dogs Langston et al. (7) produced sustained hypertension with a combination of subtotal nephrectomy and salt loading but observed only small increases in arterial pressure following either subtotal nephrectomy without salt loading or salt loading without subtotal nephrectomy. Glomerular filtration rate was reduced to 34% of control following subtotal nephrectomy and to 45% of control during the salt-loading period. Using the same preparation Douglas et al. (8) demonstrated that transient increases in blood volume, sodium space, and interstitial fluid pressure occur at the onset of the hypertension. The present study was designed to test in this preparation specifically whether or not a transient increase in cardiac output also occurs at the onset of salt-loading hypertension and whether or not this could be the basis of an autoregulatory rise in arterial pressure. Simultaneous measurements of other transients possibly important to understanding the pathogenesis of the hypertension were also made.

Methods

SURGICAL PREPARATION

Mongrel dogs weighing an average of 18 kg were used. Surgical preparation consisted of a series of two operations to remove renal mass separated by a recovery period. The first operation consisted of surgically removing an estimated 40% of the right kidney. The kidney was exposed through a flank incision, and the entire renal pedicle was temporarily ligated. The poles of the kidney were excised, and large bleeders were subsequently cauterized. The temporary ligature was removed, and the kidney was restored to its original position. Care was taken to interrupt renal blood flow for no more than 2 minutes.

The second operation was performed after a 10-day to 3-week recovery period and consisted of removing the left kidney and threading number-15 siliconized vinyl catheters into the right atrium and aorta through the renal vein and artery of the removed kidney. The external ends of the catheters were brought out between the animal's shoulders.

Animals were maintained on 1 to 2 lbs of commercially available canned dog food per day throughout the experiment.

SALT-LOADING PROTOCOL

The experiment consisted of (1) a baseline period beginning approximately 10 days following the second preparatory operation and (2) a period of increased salt and water intake following the baseline period. The animals were divided into two groups, one group of five animals was observed during a baseline period of 7 days and was then given an unrestricted amount of isotonic saline in lieu of drinking water for a period of 2 weeks. Arterial pressure, cardiac output, and heart rate were measured approximately every second day during the experiment. A second group of six animals was observed during an 8-day baseline period followed by a 13-day period of increased salt and water intake. During this period, isotonic saline was continuously infused through the animal's right atrial catheter. The animal was connected to the infusion apparatus by an umbilical cord that consisted of vinyl tubing covered with a protective outer shell of gum rubber. The cord was connected on one end to a cloth jacket worn by the animal and on the other end to a swivel and spring apparatus. The specially constructed swivel afforded the animal rotational movement, while the spring allowed the cord to extend when the animal was lying and retracted the cord when the animal was standing. Saline infusion rate from

an overhead reservoir was controlled either by a thumbwheel resistance or a Holter Company roller pump. Arterial pressure, cardiac output, heart rate, right atrial pressure, blood urea nitrogen, serum sodium, and serum potassium were measured approximately every second day during the experiment. The animals were allowed no drinking water.

INSTRUMENTATION

All permanent records were made on a Model 1108 Visicorder. Arterial and right atrial pressures were measured using Statham strain-gauge transducers. Cardiac output was determined by dye-dilution procedures. Cardio-Green dye (supplied by Hynson, Westcott, and Dunning, Baltimore, Maryland), a Gilford Model 103IR cuvette densitometer, and a Gilford Model 105A constant flow system were used. To minimize the effects of the laboratory environment on the arterial pressure and cardiac output determinations, all measurements were made between 8 and 12 AM, and the animals were allowed to rest quietly for 15 to 30 minutes before the measurements were started. Reported cardiac output values are averages of triplicate determinations. Heart rate was determined from arterial records by counting the number of pressure pulses occurring in a 20-second interval. Serum chemistry was done on a Technicon Auto-analyzer. Stroke volume was calculated from cardiac output and heart rate measurements, and peripheral resistance was approximated from arterial pressure and cardiac output measurements.

Results

ANIMALS DRINKING SALINE

The effects of giving a group of five partially nephrectomized dogs saline in lieu of drinking water are shown in Figure 1. The saline drinking period lasted 14 days, and average saline consumption was 1.8 liters/day/dog (95 ml/kg/day/dog) during this period. Arterial pressure increased during the infusion period to approximately 140 mm Hg and remained significantly elevated above the control value during the saline drinking period. Average cardiac output for the group initially increased, reaching a maximum of 140 ± 14.5% of control on the fourth day of saline drinking, and subsequently decreased toward its control level. Heart rate was unstable during the duration of the saline drinking period, but did not change significantly. Peripheral resistance initially decreased, reaching a minimum of 84 ± 14% of control on the fourth day of saline drinking, and then subsequently increased to a level significantly above control. Stroke volume initially increased, reaching a maximum of 168 ± 40.5% of control on the fourth day of the saline drinking period, and then subsequently decreased toward the control level.

TABLE 1

Deviations from Control Values and Their Statistical Significance in Five Partially Nephrectomized Dogs after Administration of 0.9% Saline in Lieu of Drinking Water

	Days 1 through 6	Days 7 through 15
Arterial pressure (mm Hg)	+21 $P < 0.001$	+27 $P < 0.001$
Cardiac output (% change)	+25.8 $P < 0.001$	+7.7 NS
Heart rate (% change)	−6.6 NS	+2.6 NS
Total peripheral resistance (% change)	−3.5 NS	+15.5 $P < 0.05$
Stroke volume (% change)	+38.2 $P < 0.001$	+14.7 NS

NS = not significant.

A summary of deviations from control values and their levels of significance are given in Table 1.

ANIMALS INFUSED WITH SALINE

The effects of continuously infusing a group of six partially nephrectomized dogs with isotonic saline are shown in Figure 2. The infusion period lasted 13 days, and average saline infusion was 3.72 liters/day/dog (191 ml/kg/day/dog) during this period. Arterial pressure increased to approximately 140 mm Hg during the infusion period and remained significantly elevated above the control value of 105 ± 2.0 mm Hg. Average cardiac output increased to a maximum of 129% of control on the third day of infusion and then decreased toward control levels. Heart rate decreased significantly during infusion, reaching a minimum of 69 ± 5.7% of control on the sixth day of infusion. Total peripheral resistance fell to a

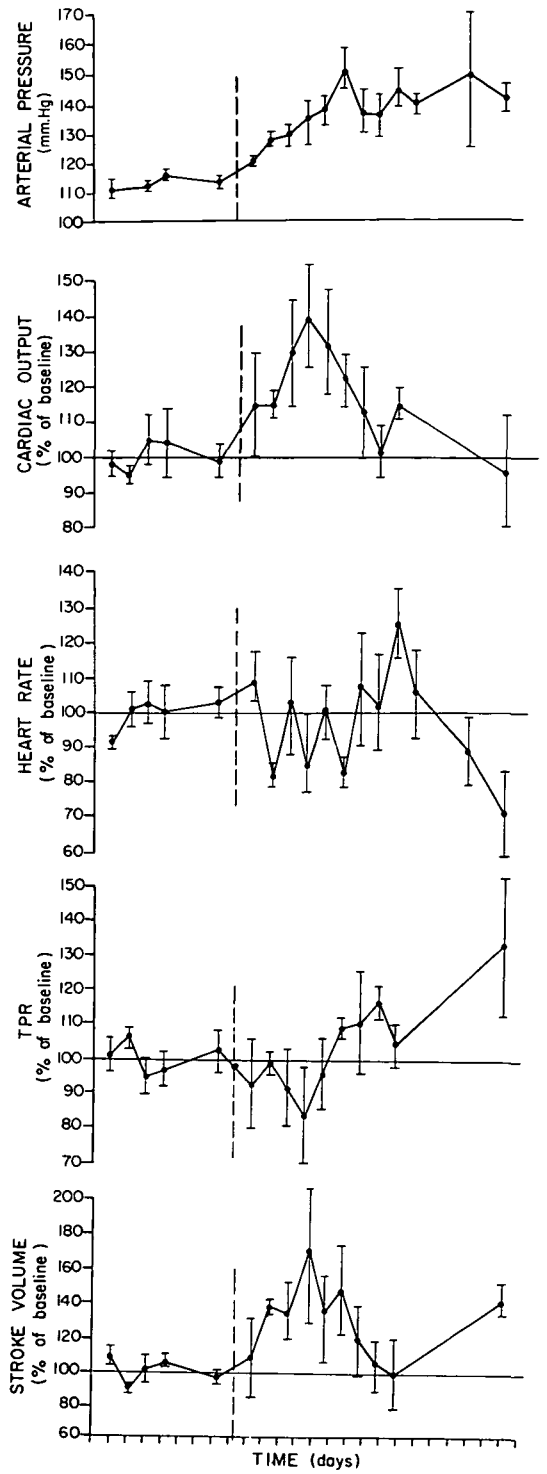

FIGURE 1

Average mean arterial pressure, cardiac output, heart rate, total peripheral resistance (TPR), *and stroke volume of five partially nephrectomized dogs given saline in lieu of drinking water. The dashed line marks the start of the administration of 0.9% saline. Vertical bars represent ±1* SEM.

minimum value of 90 ± 4.3% of control on the second day of infusion and then increased to levels significantly above control. Stroke volume was elevated during the infusion period, increasing to a maximum of 167 ± 17.5% of baseline on the sixth day of the infusion period and then decreasing toward its control level. Blood urea nitrogen fell from a baseline average of 29.8 ± 2.2 mg/100 ml to an average of 18.7 ± 12 mg/100 ml during the last 7 days of the infusion period. This decrease accompanied the marked diuresis that resulted from the increased salt and water load. A significant increase in serum sodium concentration above a control value of 144 mEq/liter was observed during the first 5 days of infusion. Serum potassium concentrations did not vary significantly from the 4.4 mEq/liter control value. Right atrial pressure increased to an average of 3.73 ± 0.48 mm Hg above the baseline on the second day of infusion but fell to an average of 1.87 ± 0.29 mm Hg above control during the last 4 days of the infusion period.

A summary of deviations from control values and their levels of significance are given in Table 2.

Discussion

These studies have demonstrated a persisting elevation in arterial pressure but only transient increases in cardiac output and stroke volume following salt and water loading. In general, the responses of dogs drinking saline were much more irregular than those of dogs infused continuously with saline, although both the saline drinking group and the infused group showed similar trends. In a number of instances, deviations from control values were statistically significant in the infused group but not in the saline drinking group. This variability was probably caused by the fact that, when saline is offered to an animal ad lib, daily intake rates can be extremely irregular, ranging from 0 to 4 or 5 liters/day. Some irregularity in the data

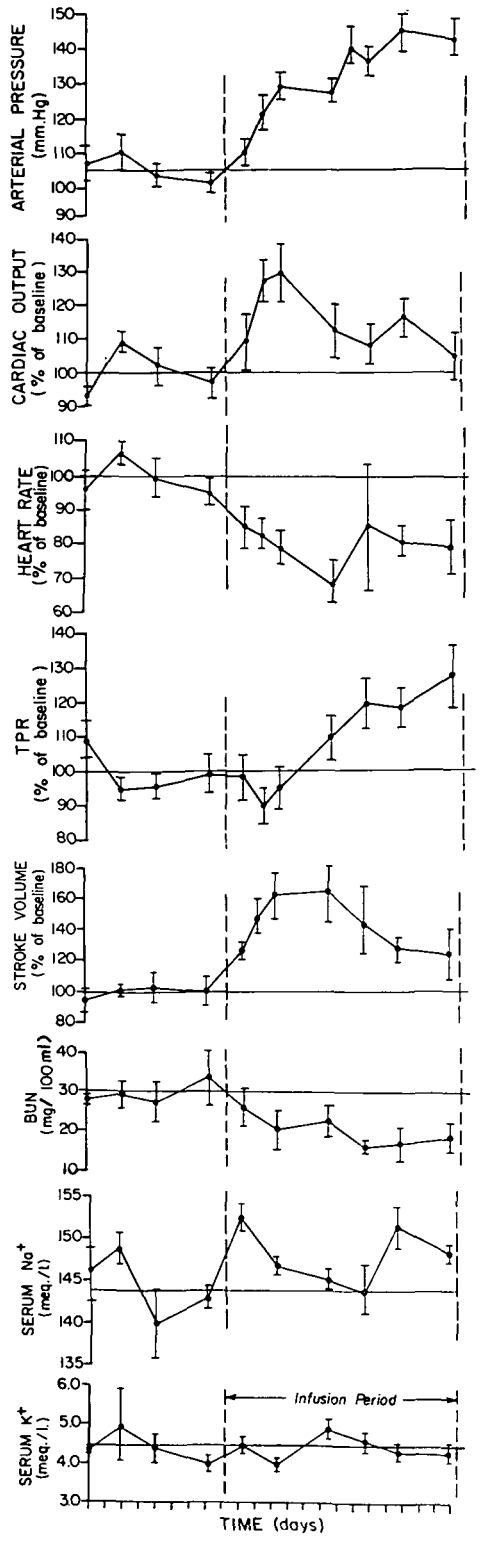

FIGURE 2

Average mean arterial pressure, cardiac output, heart rate, peripheral resistance, stroke volume, blood urea nitrogen (BUN), serum sodium, and serum potassium of six partially nephrectomized dogs infused with 0.9% saline.

TABLE 2

Deviations from Control Values and Their Statistical Significance in Six Partially Nephrectomized Dogs Infused with 0.9% Saline

	Days 1 through 5	Days 6 through 13
Arterial pressure (mm Hg)	+16.3 $P < 0.001$	+35.1 $P < 0.001$
Cardiac output (% change)	+22 $P < 0.001$	+11.9 $P < 0.01$
Heart rate (% change)	−17.6 $P < 0.001$	−21.5 $P < 0.001$
Total peripheral resistance (% change)	−5.6 NS	+17.1 $P < 0.001$
Stroke volume (% change)	+48 $P < 0.001$	+47.1 $P < 0.001$
Blood urea nitrogen concentration (mg/100 ml)	−7.0 NS	−10.9 $P < 0.001$
Serum sodium concentration (mEq/liter)	+5.7 $P < 0.01$	+2.6 NS
Serum potassium concentration (mEq/liter)	−0.2 NS	+0.1 NS

NS = not significant.

describing circulatory function then would not be unexpected.

Though a number of different theories might be formulated to explain the transient effects observed in the present studies, one that we believe to fit the data best, and one that has considerable evidence in its favor is the following: (1) Excess water and salt loading causes an increase in extracellular fluid volume, accounting for the 30% transient increase found by Douglas et al. (8) during the first week of this type of hypertension. (2) A portion of the extracellular fluid presumably remains in the circulatory system, accounting for the 20% transient increase in blood volume also found by Douglas. (3) The increase in

blood volume presumably increases the mean systemic pressure in accordance with the studies of Richardson et al. (9), who earlier showed that there is a direct relationship between blood volume and the "filling" pressure (mean systemic pressure) of the circulation. (4) The increase in mean systemic pressure theoretically increases venous return of blood to the heart (an effect that has been studied previously in this laboratory [10]), thereby increasing the right atrial pressure. (5) The increase in right atrial pressure causes an increase in stroke volume output in accordance with the Frank-Starling law of the heart. (6) The increase in stroke volume output causes an increase in the cardiac output. (7) Increase in cardiac output elevates the arterial pressure. (8) The elevation of arterial pressure induces a baroreceptor reflex which reduces heart rate. (9) The increase in arterial pressure also stretches the small arteries, thereby reducing the total peripheral resistance, as shown by Green and Rapela (11), during the first few days of the rise in arterial pressure. Also, the baroreceptor reflex caused by the initial rise in pressure due to increased cardiac output would be expected to reduce further the total peripheral resistance. (10) If long-term autoregulation occurs in the entire body and develops gradually over a period of days, the increase in blood flow through the tissues would be expected to cause a gradual increase in total peripheral resistance, such as was seen after the first 3 days of these experiments. However, this step in the sequence of events hinges upon proof that such autoregulation as this can occur. (11) The increasing total peripheral resistance further enhances the arterial pressure but concomitantly reduces venous return, thereby reducing the cardiac output back toward normal. Therefore, the elevated arterial pressure thereafter is sustained primarily by increased total peripheral resistance rather than increased cardiac output. (12) The increased arteriolar resistance that causes the increase in total peripheral resistance reduces capillary pressure, which causes reabsorption of interstitial fluid that had earlier leaked into the interstitial spaces. (13) The elevated arterial pressure increases glomerular filtration pressure and thereby causes loss of extra fluid from the circulation (12), returning the fluid volumes back toward normal. (14) The baroreceptors gradually reset to the increased arterial pressure level (13, 14) causing heart rate to increase toward normal which in turn causes stroke volume to decrease toward normal.

Each of the above steps in the postulated sequence, with the exception of long-term, whole-body autoregulation, has solid substantiation. Therefore, plausibility of the entire theory rests upon being able to show that long-term, whole-body autoregulation does indeed occur. It is certain that this is not merely the acute autoregulation of the usual type seen in muscle and other tissues within seconds to minutes following increased flow. Acute autoregulation occurs much too rapidly and is not of enough magnitude to cause the several-day transient events recorded in the present experiments. Folkow (15) more than a dozen years ago demonstrated in whole kittens perfused by larger cats that the entire body can autoregulate acutely but only to a very mild degree, and in our laboratory we have confirmed this in the perfused, headless, and spinal cord-denervated dog (unpublished results).

Yet, there is reason to believe that long-term, whole-body autoregulation, taking place over a period of hours and days, can gradually elicit enough increase in total peripheral resistance to cause return of cardiac output almost to the control level while sustaining the hypertension. This would require only 35% increase in resistance, which is not a severe requirement. An observation that leads one to believe that at least this much increase in resistance can occur under the influence of excess blood flow through the peripheral tissues was that of Conway (16), who demonstrated that acutely increased blood volume in a dog causes a marked rise in cardiac output but little immediate increase in arterial pressure. However, the cardiac output fell over a period of hours while the peripheral

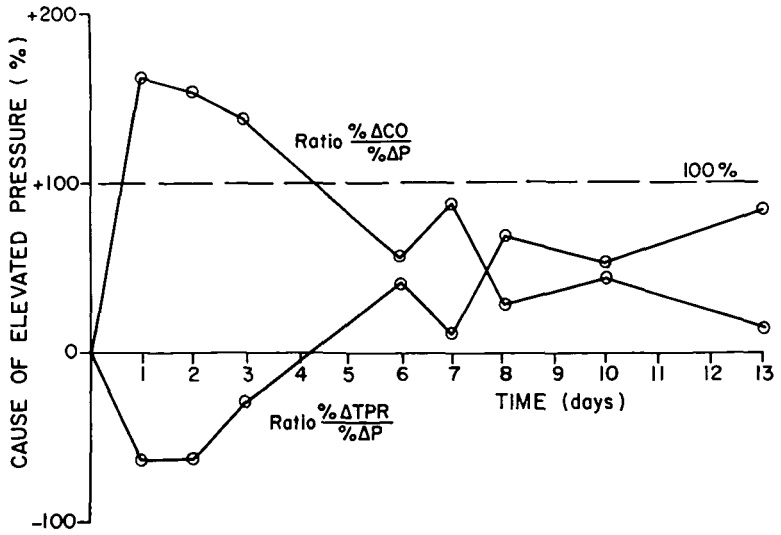

FIGURE 3

The relative importance of cardiac output (CO) *and total peripheral resistance* (TPR) *in elevating arterial pressure* (P) *in partially nephrectomized dogs infused with isotonic saline.*

resistance and arterial pressure continued to rise. Another pertinent study was that of Patterson et al. (17) who showed that blood flow in the upper part of the body in persons with coarctation of the aorta is entirely normal, indicating adjustment of the vascular resistance in proportion to the rise in pressure. That this increase in resistance is locally induced was indicated by the fact that resistance was *not* increased in the lower part of the body. A similar response in the dogs of the present study could explain the interrelationships observed between pressure, flow, and resistance at the onset of salt-induced hypertension.

Figure 3 illustrates quantitatively the relative contributions of cardiac output and peripheral resistance to the increased arterial pressure in the dogs infused with isotonic saline. The results are expressed as the ratio of increase in cardiac output or peripheral resistance to increase in arterial pressure. Note that during the first few days all of the rise in arterial pressure was caused by elevated cardiac output. During this period the total peripheral resistance actually fell below control values, presumably because the rising arterial pressure caused dilatation of the arterioles. However, as the pressure became stabilized at hypertensive levels, most of the pressure elevation was then caused by increased total peripheral resistance while the effect of cardiac output had fallen to very little. The temporal sequence shown in this figure agrees almost exactly with previous mathematical analyses of circulatory function (18) and is consistent with the concept (a) that salt-induced hypertension is initiated primarily by elevation in cardiac output and (b) that the rise in total peripheral resistance is a late development, possibly resulting secondarily from the rise in cardiac output.

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THOMAS G. COLEMAN and ARTHUR C. GUYTON

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