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Hemodynamic, Fluid, and Electrolyte Changes during Sodium Depletion in Conscious Dogs (40789)

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Sodium depletion is a powerful stimulus to increase the release of renin by the kidney. It has been suggested that during sodium depletion a decrease in cardiac output activates the renin–angiotensin system and that angiotensin II provides an important compensatory mechanism to maintain arterial pressure in the presence of decreased cardiac output (1, 2). Also, in dogs with thoracic caval constriction, a model for low output heart failure, a decrease in cardiac output is known to be accompanied by a high plasma renin activity (PRA), an increase in total peripheral resistance, and maintenance of arterial pressure unless circulatory failure is severe (1, 3). Most investigators have found no change in arterial pressure during sodium depletion but some controversy exists on the changes in cardiac output which occur. Mimran, Guiod, and Hollenberg (4) reported a decrease in cardiac output following sodium depletion in anesthetized rabbits, and Liang, Gavras, and Hood (5) found a decrease in cardiac output in sodium-depleted dogs sedated with morphine sulfate. On the other hand, Coleman *et al.* (6) failed to find a change in cardiac output following sodium depletion in anesthetized rats. Since it is difficult to achieve the same level of anesthesia or sedation in sodium-depleted animals as in normals and since cardiovascular function is dependent upon the level of anesthesia, it was decided to examine the changes occurring during sodium depletion in trained conscious dogs; hemodynamic, body fluid volume, and electrolyte changes produced during sodium depletion and subsequent sodium repletion were studied. It was imperative to study the animals during a recovery phase to demonstrate that the fall in cardiac output was not the result of training. Indeed, in preliminary studies a progressive fall in cardiac output was observed with training so that in the definitive study, sodium depletion was not accomplished until cardiac output was stable. The observations during the volume repletion of the recovery period provided an opportunity to evaluate the concept of whole body autoregulation.

Materials and methods. Calm female hounds weighing 18–24 kg (average weight, 20.6 kg) were selected for this study. All experiments were performed in conscious animals which had been trained for 2 to 4 weeks to lie quietly on a padded table. At least 7 days before data collection the animals were splenectomized and chronic catheters were placed in the aortic arch through the right carotid artery and in either the superior vena cava or right heart through the right external jugular vein. The catheters were exteriorized at the back of the neck. During the acute studies, blood pressure was recorded continuously from the chronic arterial catheter with a Statham P23Db pressure transducer and a Sanborn 7700 recorder. Heart rate was determined from the blood pressure recording. Cardiac output was determined by dye dilution using indocyanine green dye; each value is the mean of three determinations made in rapid succession. Stroke volume was calculated by dividing cardiac output by heart rate. Plasma volume was estimated by injection of Evans blue dye. Hemtocrit was measured by a microhematocrit method and plasma sodium and potassium concentrations were determined by flame photometry. For plasma renin activity (PRA), blood samples were collected in chilled tubes containing 0.1 ml of 10% ethylenediaminetetraacetate (EDTA) per 10

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ml of blood. The tubes were centrifuged in the cold for plasma separation. The plasma was prepared for angiotensin I generation by dialysis against a phosphate buffer (pH 5.4) for 18 hr (three changes) after which diisopropylfluorophosphate (DFP) and sodium chloride were added. The plasma was incubated for 60 min at 37°C and placed in ice water to stop the reaction. Angiotensin I (AI) content was determined by radioimmunoassay (7).

Prior to data collection the dogs were maintained for at least 6 days on a diet containing 60 meq sodium and 50 meq potassium daily. Throughout the study water was available *ad libitum* and the volume consumed daily was recorded. The animals were housed in metabolic cages to allow measurement of fluid and electrolyte balances. After the 6-day period on the normal diet, the dogs were placed on a padded table for approximately 90 min during which blood pressure was continuously recorded. After blood pressure and heart rate stabilized, cardiac output and plasma volume were measured. Heart rate was determined immediately before and after the cardiac output and the average of the two values recorded. Arterial blood samples were also taken for determination of PRA, hematocrit, and plasma sodium and potassium concentrations. The same procedure was repeated so that three series of control values were obtained 2 days apart for each dog. After these sodium replete measurements, the dogs were sodium depleted by maintenance on a low sodium diet (<3 meq/day) and intramuscular injections of 2 cm^3 Mercuhydrin on the first 2 days of the low sodium diet. This regimen resulted in an average sodium loss of 121 meq over the first 4 days. After initiation of the sodium depletion, measurements of blood pressure, cardiac output, heart rate, plasma volume, PRA, hematocrit, plasma sodium, and potassium concentrations were repeated three times, each of which was 2 days apart; the same procedures were utilized as previously described. In order to be certain that the changes observed with sodium depletion were not due to training, the dogs were returned to the normal diet (60 meq Na, 50 meq K, daily) and after sodium repletion, three more series of hemodynamic measurements were made. All data were analyzed using analysis of variance and the Newman–Keuls multiple range test.

Results. Hemodynamic measurements were made in six dogs on a normal sodium intake, during sodium depletion, and after return to the normal sodium diet. During the early training periods, the hemodynamic parameters were variable but with training they became much more stable and lower. The study was not undertaken until it was certain that these functions were stable and that the dogs were relaxed and accustomed to the measurement procedures. Table I presents the hemodynamic responses to sodium depletion and subsequent sodium repletion in the conscious dogs.

During sodium depletion heart rate increased from control sodium replete values of 71, 73, and 77 beats/min to 89, 90, and 94 beats/min ($P < 0.01$) and stroke volume fell from control values of 33.0, 32.7, and 32.0 ml to 21.3, 22.3, and 21.5 ml ($P < 0.01$). The fall in stroke volume was not totally offset by the increased heart rate and resulted in a fall in cardiac output from control values of 2.30, 2.29, and 2.37 liters/min to 1.85, 1.90 and 1.87 liters/min (<0.01). This fall in cardiac output during sodium depletion was accompanied by an increase in peripheral resistance from 42.5, 41.8, and 40.3 mm Hg $(liters/min)^{-1}$ to 50.2, 48.9, and 48.4 mm Hg $(liters/min)^{-1}$ ($P < 0.01$). The increase in peripheral resistance sustained the arterial pressure at 89, 90, and 88 mm Hg which was not significantly different from the control levels of 94, 93, and 92 mm Hg despite the fall in cardiac output. Plasma volume failed to decrease significantly from the control values but the values of 1083, 1121, and 1098 ml during sodium depletion were less ($P < 0.05$) than the recovery level.

Subsequently, the dogs were returned to the normal control diet (60 meq Na and 50 meq K daily) and 1 week later the hemodynamic measurements were repeated. This volume repletion provided a forcing to challenge the animals to achieve whole body autoregulation and to increase

TABLE I. HEMODYNAMIC CHANGES IN TRAINED, CONSCIOUS DOGS DURING SODIUM DEPLETION AND REPLETION (means ± SEM; $N = 6$)

Day	Mean arterial pressure (mm Hg)	Heart rate (beats/min)	Cardiac output (liters/min)	Stroke volume (ml)	Peripheral resistance [mm Hg (liters/min)$^{-1}$]	Plasma volume (ml)
6	94 ± 4	71 ± 6	2.30 ± 0.20	33.0 ± 3.5	42.5 ± 3.8	1201 ± 60
8	93 ± 3	73 ± 7	2.29 ± 0.16	32.7 ± 3.6	41.8 ± 3.3	1193 ± 72
10	92 ± 3	77 ± 6	2.37 ± 0.19	32.0 ± 4.0	40.3 ± 4.4	1224 ± 67
11	Start sodium depletion regimen					
14	89 ± 2	89 ± 6**	1.85 ± 0.19**	21.3 ± 2.4**	50.2 ± 3.9**	1083 ± 52*
16	90 ± 2	90 ± 9**	1.90 ± 0.16**	22.3 ± 3.3**	48.9 ± 3.5**	1121 ± 60*
18	88 ± 3	94 ± 10**	1.87 ± 0.17**	21.5 ± 2.7**	48.4 ± 3.7**	1098 ± 53*
19	Start normal sodium diet					
25	89 ± 2	74 ± 5	2.29 ± 0.20	31.1 ± 2.6	40.3 ± 3.5	1236 ± 94
27	88 ± 3	71 ± 4	2.26 ± 0.19	32.5 ± 3.8	40.0 ± 3.1	1294 ± 58
29	87 ± 2	74 ± 5	2.28 ± 0.17	31.5 ± 3.2	39.3 ± 3.4	1306 ± 58

* $P < 0.05$ compared to recovery data (Days 25, 27, 29).
** $P < 0.01$ compared to control and recovery data.

their arterial pressure. Heart rate fell to 74, 71, and 74 beats/min, values which are not different from the control, sodium replete values. Stroke volume and cardiac output increased to levels of 31.1, 32.5, and 31.5 ml and 2.29, 2.26, and 2.28 liters/min, respectively; these values were not significantly different from controls. Peripheral resistance returned to levels of 40.3, 40.0, and 39.3 mm Hg (liters/min)$^{-1}$ which were similar to controls and blood pressure remained unchanged at 89, 88, and 87 mm Hg. After sodium repletion, plasma volume increased to levels of 1236, 1294, and 1306 ml which were indistinguishable from controls. Consequently, during the recovery period the peripheral arterioles dilated and did not respond in accordance with the theory of whole body autoregulation.

The control, sodium replete PRA values were 0.73, 0.92, and 0.85 ng angiotensin I/ml/hr (ng AI/ml/hr); these are typical of those observed previously in this laboratory. During sodium depletion PRA increased to 7.58, 7.10, and 7.59 ng AI/ml/hr ($P < 0.01$). With sodium depletion, PRA returned to levels of 0.94, 0.86, and 0.83 ng AI/ml/hr. After initiation of the low sodium diet, water intake was elevated from the control level of 307–555 ml/day to 767–1055 ml/day on 6 of the 8 days of sodium depletion ($P < 0.01$ to 0.05). Urine volume was also increased from 388–543 ml/day to 702–1003 ml/day on 5 of the 8 days of sodium depletion ($P < 0.01$ to 0.05) and a positive water balance was observed during the latter part of the period of sodium depletion ($P < 0.01$). After the high sodium excretion produced during the 2 days of Mercuhydrin administration, daily urinary sodium excretion was low. During sodium depletion, plasma sodium concentration was decreased in two of the three measurements ($P < 0.01$ and 0.05) and plasma potassium concentration was increased on two of the three occasions ($P < 0.01$ and 0.05). Following sodium repletion, sodium and water balances and plasma sodium and potassium concentrations returned to the normal control level.

Discussion. The present study was undertaken to determine the changes in cardiovascular hemodynamic function which result during sodium depletion. The observations were made in trained, conscious dogs so that the effects of anesthesia or excitement could be excluded. It is well known that anesthesia alters cardiovascular function and it is almost impossible to achieve comparable levels of anesthesia in animals with a compromised circulation and in normal controls. The present trained dogs were in a basal state as indicated by the low and reproducible values obtained in triplicate for arterial pressure, heart rate, and cardiac output during the control and recovery periods. Also, a steady state was achieved during sodium depletion because

the values for heart rate, cardiac output, stroke volume, and peripheral resistance were very similar during the three separate measurements.

It is important to emphasize that in this type of study in conscious dogs it is imperative to make recovery observations. In preliminary studies, it was found that cardiac output fell progressively with training; when the animals were sodium depleted before training was adequate to achieve a stable state, part of the reduced cardiac output was attributable to training rather than the sodium depletion. By sodium and volume repleting the animals and obtaining recovery observations, the presently observed decrease in cardiac output was related to the sodium-depleted state alone. Bravo and Tarazi (8) have previously reported that cardiac output was reduced in conscious sodium-depleted dogs but no evidence was presented to show that steady state conditions were achieved during the control period and no recovery observations were made. Failure of heart rate to increase during sodium depletion in their study (8) while heart rate increased from 74 to 91 beats/min in the present study might reflect inadequate training of their dogs. Consequently, the present data provide the first definitive demonstration that cardiac output is decreased during sodium depletion of normal conscious animals. The present results are consistent with an earlier report from this laboratory that cardiac output fell in conscious, sodium-depleted, one-kidney hypertensive dogs (9).

Mimran *et al.* (4) and Liang *et al.* (5) have reported falls in cardiac output with sodium depletion in anesthetized rabbits and morphine-sedated dogs, respectively. Since the depth of anesthesia can influence the level of cardiac output, it is difficult to interpret data of this type in which the changes were small. It is noteworthy that in the study of Liang *et al.* (5), no change in heart rate was observed. The present results are not in agreement with those of Coleman and colleagues (6) who failed to find a change in cardiac output with sodium depletion in anesthetized rats. This difference in results from the present findings might reflect a lesser degree of sodium depletion or an influence of anesthesia.

In the present study, the degree of sodium depletion averaged 121 meq of sodium over the first 4 days. Plasma volume appeared to decrease with sodium depletion but $P > 0.05$; however, plasma volume during sodium depletion was significantly lower than during the recovery period ($P < 0.05$). During sodium depletion heart rate increased from 74 to 91 beats/min., a 23% increase, while stroke volume fell 33%. The tachycardia might be a compensatory mechanism secondary to the increased activity of the sympathetic nervous system which occurs in low output states such as sodium depletion (10, 11) and congestive heart failure (12). Several lines of convincing evidence for increased activity of the sympathetic nervous system in sodium-depleted man were first presented by Gordon *et al.* (10) in 1967; recently, Robertson *et al.* (11) reported that both plasma norepinephrine and urinary normetanephrine were increased in patients on a 10-meq/day sodium diet in comparison with results on a 150-meq/day sodium diet.

Another compensatory mechanism is the increase in peripheral resistance which maintained arterial pressure at the control level in the presence of reduced cardiac output. The mechanisms responsible for this increase in peripheral resistance probably include both an action of angiotensin II on the smooth muscle of the arterioles and a reflex action of the sympathetic nervous system to maintain peripheral arteriolar tone. This compensatory action of angiotensin II has been demonstrated previously (1) by use of angiotensin blockade during sodium depletion. The compensatory increase in peripheral resistance with the maintenance of arterial pressure in sodium depletion also occurs in response to a fall in cardiac output in dogs with thoracic caval constriction, a model for low output heart failure (1). It is of interest that the kidney plays a key role in this increase in peripheral resistance which occurs during sodium depletion and thoracic caval constriction; again, this was observed during antiotensin blockade (13).

An important incidental finding was obtained during the recovery observations. With the sodium and volume repletion and volume expansion during the recovery pe-

riod, the animals had an increase in cardiac output so the peripheral arterioles were presented with an opportunity to constrict and to exhibit the phenomenon of whole body autoregulation. Instead, the peripheral arterioles dilated and no evidence for whole body autoregulation was observed.

Summary. Hemodynamic, fluid and electrolyte changes were studied during sodium depletion and repletion in six conscious dogs. Blood pressure (BP), plasma renin activity (PRA), heart rate (HR), cardiac output (CO), stroke volume (SV), and plasma volume (PV) were determined on 3 separate days in sodium replete conscious animals, similarly during sodium depletion, and again after sodium repletion. During sodium depletion, HR increased from 73 to 91 beats/min ($P < 0.01$). CO fell from 2.32 liters/min to 1.87 liters/min ($P < 0.01$). SV decreased from 32.6 ml to 21.7 ml ($P < 0.01$). Peripheral resistance (PR) increased from 41.5 to 49.2 mm Hg (liters/min)$^{-1}$ ($P < 0.01$). BP was unchanged. PRA increased from 0.83 to 7.51 ng angiotensin I/ml/hr ($P < 0.01$). During the 8 days of sodium depletion, water intake was elevated on 6 days, urine volume was elevated on 5 days, and water balance was positive on 3 days. With sodium and volume repletion, all functions returned to control levels. The results demonstrate that sodium depletion produced significant decreases in CO and PV with BP maintained by increased PR and HR. An important incidental finding was the failure of whole body autoregulation to occur during the sodium and volume repletion and volume expansion of the recovery period.

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