Cardiac Output and Peripheral Resistance in Strains of Rats Sensitive and Resistant to NaCl Hypertension

MUKUL GANGULI, D.V.M., PH.D., LOUIS TOBIAN, M.D., AND JUNICHI IWAI, M.D.

SUMMARY The interrelationship of blood pressure, cardiac output, and peripheral resistance was studied in Dahl "S" and "R" rats after 3 days on a high (8%) NaCl diet. Both "S" and "R" rats were nonhypertensive when fed a normal (0.3%) NaCl diet. After 3 days of the high NaCl diet, the "R" rats remained normotensive (BP 112 mm Hg), while the "S" rats had an elevation of arterial pressure (BP 133 mm Hg) (p < 0.001). The cardiac outputs of both "S" and "R" rats were similar on the low NaCl diet. After 3 days of high NaCl feeding, the cardiac output of the "R" rats rose 18% above the "R" control level (p < 0.0001), while the peripheral resistance declined 14% below the "R" control level (p < 0.005), and the blood pressure (BP) did not change, a pattern quite contrary to the concept of "whole-body" autoregulation. With a similar 3-day high NaCl feeding in "S" rats, cardiac output (p < 0.005) and peripheral resistance (p < 0.05) both increased 10%, while BP rose 20%. After 7 days of high NaCl feeding, the cardiac output of the "S" rats had returned to normal, while blood pressure and peripheral resistance both continued to be elevated. This pattern of response in "S" rats could be compatible with the concept of "whole-body" autoregulation. However, since both NaCl hypertension and Goldblatt hypertension can occur in settings in which "whole-body" autoregulation appears not to be causally related, one cannot be certain whether "whole-body" autoregulation is playing a causal role in the mechanism of NaCl-induced hypertension in "S" rats. It is a striking dichotomy that 3 days of high salt feeding produces vasoconstriction in "S" rats and vasodilation in "R" rats. (Hypertension 1: 3-7, 1979)

KEY WORDS • cardiac output • salt hypertension • blood pressure • diet • peripheral resistance • "whole-body" autoregulation

There is evidence that experimental hypertension may be associated with a transient initial increase in cardiac output as part of the mechanism. Moreover, saline loading tends to increase cardiac output.

The relationship of sodium intake to human hypertension is another area in the pathogenesis of hypertension that has never been fully explained. Primitive inland societies with a very low sodium intake have virtually no hypertension and even avoid the usual rise in blood pressure with advancing age. On the other hand, another primitive society that cooks its food in salty sea water is known to have its share of essential hypertension. Moreover, whenever members of sodium-deprived primitive societies move to cities and begin eating the large amount of salt that accompanies acculturation, they invariably begin to have an increased incidence of hypertension. A reasonable hypothesis to account for this pattern could be as follows: if the hereditary predisposition for hypertension is present, a life-long avoidance of salt may prevent the hypertension from ever making an appearance, while on the other hand, a generous daily intake of salt allows the rise of blood pressure to occur. If the hereditary predisposition for hypertension is absent, then the blood pressure will be normal even though the subject is consuming a sizable intake of NaCl.

In this study, we were seeking physiologic explanations for the interactions of salt, heredity, cardiac output and peripheral resistance in the causation of hypertension. In this quest, we used the Dahl "S" and "R" strains of rats (the "R" rats being resistant and the "S" rats sensitive to NaCl hypertension). When on a low sodium intake, rats of both "S" and...
“R” strains have a blood pressure close to “normal,” reminiscent of primitive human inland societies. However, when fed a high sodium diet, the “R” strain retains its “normal” blood pressure, while the “S” strain becomes quite hypertensive, again similar to hypertensive and normotensive human subjects living in civilized societies.

Methods

A total of 178 female rats of “S” and “R” strains, about 6 weeks of age and weighing about 130 g each, were used. They were divided into eight categories and fed special diets as follows:

<table>
<thead>
<tr>
<th>Diet</th>
<th>Three-day feeding</th>
<th>Seven-day feeding</th>
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<tbody>
<tr>
<td></td>
<td>0.3% NaCl</td>
<td>0.3% NaCl</td>
</tr>
<tr>
<td>S Group I</td>
<td>(n = 28)</td>
<td>(n = 28)</td>
</tr>
<tr>
<td>S Group II</td>
<td>(n = 13)</td>
<td>(n = 13)</td>
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<tr>
<td>R Group III</td>
<td>(n = 28)</td>
<td>(n = 28)</td>
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<tr>
<td>R Group IV</td>
<td>(n = 13)</td>
<td>(n = 13)</td>
</tr>
<tr>
<td>S Group V</td>
<td>(n = 24)</td>
<td>(n = 24)</td>
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<tr>
<td>S Group VI</td>
<td>(n = 24)</td>
<td>(n = 24)</td>
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</tbody>
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These two levels of dietary NaCl, 0.3% and 8.0%, could be considered as either “normal” or “high-salt,” respectively. The two diets were similar in all respects other than NaCl content. The 0.3% NaCl pelleted diet is a mixture of a great variety of natural foodstuffs, vitamins and minerals ordinarily used in making commercial rat diets, but with no NaCl added to the mixture. The 8% NaCl diet was exactly the same as the 0.3% NaCl diet except that the NaCl was added up to 8% of the dry weight of the diet. This mixture with its added NaCl was then pelleted. All rats had received 0.3% NaCl chow since weaning. High salt feeding was carried out in both “S” and “R” rats for either 3 or 7 days. Concomitant feeding of a diet with 0.3% NaCl was carried out in other “S” and “R” rats. Since the “S” and “R” rats gained the same amount of weight on the 8% NaCl diet, one can presume that they ingested the same amount of food and NaCl. At the end of the feeding periods, the cardiac output was measured in these rats under Inactin (120 mg/kg) anesthesia, using a standard thermal dilution method. This was done as much as possible in a “round robin” fashion among Groups I–IV, and Groups V–VIII. The mean intraarterial pressure was measured directly just before the cardiac output measurement so that peripheral vascular resistance could be calculated (pressure/flow).

To measure cardiac output, the right jugular vein was cannulated with a polyethylene tube (PE 10) filled with normal saline (0.9% NaCl) containing a small amount of heparin. The tube was passed down to the entrance of the right atrium. The entire rat was then lightly heparinized. After tracheal cannulation, the left carotid artery was also cannulated and a thermistor probe (YSI No. 524) was advanced to the arch of aorta so that the tip was situated in the main stream of aortic arch blood.

Normal saline at room temperature (20°–22° C) was injected as a bolus equal to 0.07% of body weight into the right atrium, thus locally cooling the blood. The passage of this pulse of cooled blood was measured by the thermistor in the aortic arch and recorded by means of a YSI telethermometer bridge and a Grass polygraph. The thermistor was calibrated on the polygraph against a mercury thermometer accurate to 0.025° C. A typical recording is presented in figure 1. Three to four successive determinations of cardiac output within 8 to 10 minutes were performed for each rat and the values were averaged. The temperature of the injectate was measured with the same calibrated mercury thermometer accurate to 0.025° C before each injection. The cardiac output was calculated from the thermal dilution curves by a modified Stewart-Hamilton formula.

To test the reliability of this method, we varied the injectate volume in the same rat from 0.1 ml to 0.2 ml and did not affect the cardiac output as estimated by the thermal dilution technique, even though the area under the curve was much larger. The precision of the thermal dilution method in our studies made it seem quite reliable for group comparisons. Since our objective was a comparison of different groups of small 140-g rats, the thermal dilution method appeared to be more suitable for us than the dye dilution method. Our measured cardiac outputs under Inactin anesthesia are close to those found in rats by others using pentobarbital anesthesia. The cardiac output per 100 g of body weight is higher in young rats than in adult rats. In our young “R” rats (140–145 g), the cardiac output averaged around 52 ml/100 g body weight/min. Using rats slightly older than ours, Lin et al. found an average cardiac output of 46 ml/100 g/min using a thermal dilution technique; and Albrecht found an average of 46 ml/100 g/min using the dye dilution technique. Thus, our cardiac output measurements in young rats are similar to those of other investigators.

Results

Table 1 gives the cardiac output of hypertension-sensitive (“S”) rats and hypertension-resistant (“R”) rats during normal and high NaCl diets of either 3 or 7 days. After either 3 or 7 days of feeding, “R” rats on the 8% salt diet had approximately the same average blood pressure as the rats on the 0.3% diet. As expected, these rats were indeed hypertension-resistant. The “S” strain showed quite a different response. After 3 days of feeding 8% NaCl, the blood pressure averaged 133 (± 5), whereas it was only 111 (± 2) in the “S” control group eating the 0.3% NaCl diet (p < 0.001). After 7 days of eating the 8% salt diet, the blood pressure of “S” rats continued to be elevated well above the “S” control levels (p < 0.001).

However, the cardiac output responses in the “R” rats after 3 days on 8% NaCl averaged 63.2 ml/min/100 g (± 1.1) body weight; whereas they averaged only 53.5 (± 0.8) after 3 days on the 0.3% NaCl diet. Here, the 8% salt diet resulted in a significant 18% increase in cardiac output above the “R” control level (p < 0.0001). After 7 days of salt feeding, the changes were not nearly so pronounced. The “R” rats on 8% salt still had a somewhat higher cardiac output.
output, but by 7 days it was only 5% higher than that of the "R" rats on 0.3% salt (p < 0.07).

The cardiac output responses in the "S" strain were, again, quite different. The cardiac output of the hypertension-prone strain was 61.6 (± 1.8) after 3 days of 8% NaCl, compared to 55.9 (± 0.8) after 3 days of 0.3% NaCl. This was a significant 10% rise (p < 0.005) in cardiac output related to high salt feeding. After 7 days of high salt feeding, the cardiac output had reduced to the level of the "S" control group.

Table 1 also shows the changes in calculated peripheral vascular resistance during the feeding experiments. As the "R" rats consumed the 8% NaCl diet for 3 days, their average peripheral resistance went down 14% below the "R" controls, a significant difference (p < 0.005). After 7 days of 8% NaCl feeding, the peripheral resistance in "R" rats was only 3% below the "R" control level, which was not a statistically significant difference.

The peripheral resistance response was totally different in the "S" strain. After 3 days of the 8%
NaCl diet, the vascular resistance went up to 10% above the “S” control level, a significant difference ($p < 0.05$). This response is in complete contrast to the “R” rats, whose resistance dropped 14% below the “R” control level after 3 days on the 8% NaCl diet. After 7 days on the 8% NaCl diet, the “S” strain had a further increase in vascular resistance to 12% above the “S” control level, again a significant difference ($p < 0.01$). After 3 days on the 8% NaCl diet, the peripheral resistance of the “S” rats was 23% above that of the “R” rats ($p < 0.01$). After 7 days on the 8% NaCl diet, the peripheral resistance of the “S” rats was 22% above that of the “R” rats ($p < 0.001$).

**Discussion**

These young rats in the two contrasting strains had about the same level of blood pressure on the 0.3% NaCl control diet. When the 8% NaCl diet is fed to “R” rats for 3 days, the cardiac output increases 18%, but the peripheral resistance decreases 14%, and the average blood pressure remains about the same. With a similar 3-day feeding of the 8% NaCl diet, the “S” rat has a markedly different response. Its cardiac output increases 10%, and its peripheral resistance also rises about 10%, so that the resulting arterial pressure rises about 20% above control.

The “S” rats’ responses to salt feeding are somewhat similar to the response to sodium loading in the partially nephrectomized Coleman-Guyton dog. In both rat and dog models, after 3 days of Na loading, there is an increase in both cardiac output and peripheral resistance, as well as arterial pressure. After a few more days of Na loading in both models, the cardiac output has returned to normal levels, while the peripheral resistance has climbed even higher and the blood pressure continues to be elevated.

Recent data by Chrysant et al. fit with this pattern. When Kyoto normotensive (WKY) rats have been fed a high NaCl intake for 4 months, the cardiac output is elevated 66% above the WKY control level, but the peripheral resistance is 29% below WKY control levels, and the blood pressure remains normal. When Kyoto spontaneously hypertensive (SHR) rats go through the same 4 months of high NaCl feeding, cardiac output is 14% lower than that of the SHR control period (not a significant difference), and peripheral resistance is significantly increased 32.5% above the SHR control level. The arterial pressure of the salt-fed SHR rats was 20% higher than the SHR control level. Here again, salt feeding is associated with vasodilation in the Kyoto normotensive rat and vasoconstriction in the Kyoto hypertensive rat.

Mark et al. and Kirkendall et al. also have somewhat similar data on human subjects. After a control period, they fed a high NaCl intake (410 mEq per day) for 2 to 4 weeks to six normotensive human subjects and to six subjects with borderline hypertension. Blood pressures and forearm blood flows were determined in each subject. When the normotensive subjects were fed the high NaCl intake for 4 weeks, arterial pressure did not rise above control levels, but forearm blood flows rose considerably above control levels, indicating forearm vasodilatation. This pattern of response was similar to the 3-day response to salt feeding of the “R” rat. On the other hand, when the subjects with borderline hypertension were fed the high salt diet for 2 weeks, the arterial pressure rose considerably above control levels and forearm blood flow was decreased below the control level, indicating vasoconstriction. Again, this pattern of response is reminiscent of the 3-day response to salt feeding in the “S” rat.

In the several studies cited above, including the present one with “S” and “R” rats, high NaCl feeding appears to cause vasoconstriction in creatures genetically susceptible to hypertension and vasodilatation in creatures genetically resistant to hypertension. It is intriguing that the Na loading can evoke such different responses in contrasting hereditary substrates. Changes in cardiac output do not necessarily precede the vasoconstriction in those undergoing a hypertensive response. Onesti et al. permitted some extracellular fluid (ECF) volume expansion to occur in uremic subjects undergoing dialysis. In 60% of these patients, the arterial pressure and the peripheral resistance rose concomitantly without any elevation in cardiac output. Thus, when peripheral resistance rises after volume expansion, it may not be correlated with even a small rise in cardiac output. Moreover, in another 20% of these patients, volume expansion elevated cardiac output and arterial pressure concomitantly without any rise in peripheral vascular resistance.

Both of these patterns of circulatory response were also seen in dogs with mineralocorticoid hypertension produced by 17-hydroxylase inhibition in experiments by Bravo et al. In some of the dogs the hypertension was apparently sustained almost entirely by an increased cardiac output and not by an increase in peripheral resistance. In other dogs, the rise in blood pressure was entirely due to an increase in peripheral resistance. In one-fourth of the pigs made hypertensive with deoxycorticosterone by Berecek and Bohr, the hypertension was maintained entirely by a rise in cardiac output with no increase in peripheral resistance. In one-half of the pigs, the hypertension was due entirely to a rise in peripheral resistance. Still another example similar to the “R” rat was seen in the study by Bravo et al., in which dogs receiving metyrapone and a very low sodium intake had a marked rise in cardiac output of 31% accompanied by a large decrease in peripheral vascular resistance, while blood pressure remained normal.

In previously normotensive uremic human subjects on dialysis, Onesti et al. found that a sizable ECF expansion produced no significant rise in either arterial pressure or peripheral resistance. The same can be said for bilaterally nephrectomized rabbits with implants of renal medullary interstitial cells. In this study, Muirhead et al. gave such rabbits a large expansion of ECF volume without producing any significant rise in arterial pressure. Thus, in subjects, either humans, rats, or rabbits, that are thoroughly resistant to hypertension, even ECF expansion will not necessarily raise arterial pressure.
In the Dahl "S" and "R" rats, the Kyoto hypertensive and normotensive rats, and in the Iowa borderline hypertensive and normotensive human subjects, a NaCl load produces a striking contrast in circulatory response; vasoconstriction in the hypertension-prone and vasodilatation in the normotensives. The mechanisms involved in this clear-cut dichotomy of response are worth intensive future investigation. A shift in the pressure natriuresis curve in the kidney may be partially responsible for the great susceptibility to increased peripheral vasoconstriction after salt feeding in the "S" rat. The shift in the pressure natriuresis curve could create a tendency to retain sodium, whenever the normotensive "S" rat is on a high NaCl diet. This tendency toward NaCl retention could somehow trigger an increase in peripheral resistance and a rise in arterial pressure. The increase in arterial pressure would facilitate sodium excretion by the pressure natriuresis mechanism and would overcome the tendency to retain sodium. Increased pressor responses emanating from the central nervous system may also partially explain the increased vasoconstriction after NaCl feeding in the "S" rat. It is also conceivable that the baroreceptors are somehow poised to reset to a higher setting in "S" rats after a dietary NaCl increase, even though these rats have blood pressures within the normotensive range while on a low-normal NaCl diet. Then, when the "S" rat begins a high NaCl diet and the cardiac output rises, their barostats may fail to adjust with resultant vasodilation; instead vascular resistance rises. When the "R" rats' cardiac output rises after NaCl loading, their barostats allow for a fall in peripheral vascular resistance and thereby maintain a normal blood pressure. The rise in peripheral resistance in "S" rats but not in "R" rats after NaCl feeding could also conceivably be explained by a process of "whole-body" autoregulation that occurs primarily in "S" rats, but is not very active in "R" rats. This could be a possible explanation for the phenomena in the "S" rat.

References

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