Sequential Hemodynamic Changes in End-Stage Renal Disease and the Anephric State During Volume Expansion

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SUMMARY The sequence of hemodynamic events during periods of salt- and water-loading was studied in anephric patients and those with end-stage kidney disease. The 10 patients studied showed four different sequential hemodynamic patterns: 1) no significant increase in blood pressure (BP) in two patients; 2) increase in BP associated with an increase in cardiac output and without change in total peripheral resistance in two patients; 3) increase in BP associated with an increase in total peripheral resistance from the beginning without an increase in cardiac output in five patients; and 4) increase in BP associated with an initial increase in cardiac output followed by an increase in total peripheral resistance in one patient. There was a significant positive correlation between BP and blood volume and between BP and total exchangeable sodium in the patients in whom salt- and water-loading increased the BP. It is concluded that during salt- and water-loading an initial rise in cardiac output is not necessary to increase BP and that a sustained rise in cardiac output does not always increase the total peripheral resistance. Mechanisms other than whole-body autoregulation play a role in increasing BP during salt- and water-loading in patients deprived of renal excretory function. (Hypertension 2: 102–110, 1980)

KEY WORDS • blood pressure • cardiac output • total peripheral resistance • volume expansion • end-stage renal disease • whole-body autoregulation

HYPERTENSION in anephric patients and those with end-stage kidney disease is sustained by a high total peripheral resistance.1, 2 In patients with end-stage kidney disease, the most important factor responsible for this increase in total peripheral resistance are the vasopressor function of the kidneys1, 2 and the increase in body salt and water.2-4 In anephric patients, salt and water balance plays a major role in the regulation of BP.2, 3-8 The final effect of salt- and water-loading in anephric patients has been found to be an increase in total peripheral resistance.5, 8 The precise mechanism by which expansion of body fluid increases BP remains uncertain, however.5, 8

In our previous experience with weekly hemodynamic studies, the BP increase induced by salt- and water-loading was associated with an increase in total peripheral resistance.2 Under similar experimental conditions, Coleman and co-workers8 reported that the initial hemodynamic change observed during salt- and water-loading was an increase in cardiac output; an increase in total peripheral resistance followed.8 These findings were interpreted as demonstrating that during the development of this hypertension the initial increase in cardiac output results in perfusion of tissues above their metabolic needs, which in turn elicits myogenic constriction of peripheral vessels, thereby producing an increase in total peripheral resistance.8, 10 According to this theory, the initial increase in cardiac output is the cause of hypertension, and the subsequent rise in total peripheral resistance is the result.8, 10

In dogs with subtotal nephrectomy subjected to salt- and water-loading, Coleman and Guyton11 described an initial increase in cardiac output followed by an increase in total peripheral resistance. A similar sequence of hemodynamic events has also been
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reported in different models of renal hypertension in different species.13-16 In contrast, in two-kidney, two
wrapped hypertension in rabbits, Fletcher and co-
workers17 described variable changes in cardiac output
at the onset of hypertension, with elevation of total
peripheral resistance as the final event.17 Bravo and
coworkers18 also found that sustained rises in BP dur-
ing administration of metyrapone were associated
with three different hemodynamic patterns of
response. Terris and coworkers19 reported that, in six
of seven pigs, elevations of BP induced by deoxycor-
ticosterone were entirely the result of increased total
peripheral resistance.

These conflicting data on the sequence of hemo-
dynamic events in renal hypertension and in salt-
and water-induced hypertension may be due to different
species and different pathophysiologic mechanisms in
different models. To determine the precise sequence
of hemodynamic events, we undertook our study in
anephric patients and those with end-stage renal dis-
ease during periods of salt- and water-loading. Our
hemodynamic observations were recorded daily or 3
days a week, to detect early and possibly transient
hemodynamic changes. This experimental design
identified four different patterns of hemodynamic
response to salt- and water-loading, which we reported
previously as a brief communication.20 It is the pur-
pose of the present paper to report detailed sequential
hemodynamic changes in 10 patients, their blood
volume, total exchangeable sodium, plasma renin con-
centration during volume expansion, and to discuss
the mechanisms responsible for BP regulation.

Methods

Four anephric patients and six patients with end-
stage kidney disease on maintenance hemodialysis
were studied sequentially: at stable dry control weight
(control1), during volume expansion, during the period
of sustained volume expansion, during volume deple-
tion, and again at dry control weight (control2). All
these five phases were studied in seven of the 10
patients. In the remaining three patients, only the first
three phases (control1, volume expansion, and
sustained volume expansion) were studied. All 10
patients studied were clinically stable, ambulatory,
and rehabilitated. None was on antihypertensive
therapy during the entire study period; none was in
heart failure or had any history of heart failure. Two
patients (Cases 1 and 2) had no history of hyperten-
sion and the remaining eight had a history of
hypertension. The clinical data of the 10 patients are
shown in table 1.

Seven patients underwent a hemodynamic study
three times a week immediately before each
hemodialysis. In three patients, hemodynamic studies
were done daily. During hemodialysis, desired body
weights were achieved by adjustment of ultrafiltration
pressure and infusion of 0.9% saline solution. Between
hemodialyses, body weights were controlled with ad-
justment of salt and fluid intake. The entire study
period lasted an average of 36 days.

Body weight was maintained within total range of 1
kg in each patient during the control period. At least
two control studies were performed, which lasted an
average of 1 week. During the volume expansion
phase, which lasted from 10-14 days, patients gained
weight progressively, with a mean increase of
6.9% ± 3.5% (mean ± sd) of the control body weight.
The constant volume expansion phase lasted a mean
of 16 days. The volume depletion phase lasted an
average of 10 days. When the patients' body weights
decreased to the control levels, at least two studies
were performed over a period of 1 week. Changes in
body weight of all 10 patients in each phase are shown
in table 2.

All patients studied were anemic. Their hematocrit
values averaged 20.4% ± 1.65% (mean ± sd), and
remained constant within a range of 3% during the en-
tire study.

Hemodynamic studies were performed through an
external connector inserted between the arterial and
venous ends of the arteriovenous shunt used for
hemodialysis.1 2 4 Cardiac output was determined by
the dye-dilution technique using a Gifford den-
sitometer with the injection of indocyanine green
through the venous side of the external connection.
Every cardiac output reported represents the average
of at least three determinations; variability of these
three determinations was within 5%. Arterial BP was
measured with a Statham strain gauge transducer
from the arterial side of the temporarily occluded ex-
ternal connector. Mean arterial pressure (MAP) was
obtained by electronic integration. Cardiac index (CI)
was calculated by dividing the cardiac output by body
surface area. Total peripheral resistance index (TPRI)
was calculated according to the formula:

\[
TPRI = \frac{MAP (\text{mm Hg})}{CI (\text{ml/sec/M}^2)} \times 1332,
\]

and expressed as dynes/sec/cm²/M².

Plasma volume was determined from the volume of
distribution of 5.0 μCi of 131albumin, using a 10-

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>History of hypertension</th>
<th>Condition during the study</th>
<th>Pattern</th>
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<td>2</td>
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<td>I</td>
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<td>End-stage kidneys</td>
<td>II</td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>M</td>
<td>yes</td>
<td>End-stage kidneys</td>
<td>II</td>
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<td>37</td>
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minute equilibration. Blood volume was calculated from plasma volume and large-vessel hematocrit; values of plasma volume were reproducible within 5%. Total exchangeable sodium was measured by $^{22}$Na, as previously described. Briefly, 20 μCi of $^{22}$Na was injected intravenously and a venous blood sample obtained for counting after a 24-hour equilibration period. Dialysis removed radioactivity so that each pre-mix plasma specimen had no residual radioactivity. Plasma volume and total exchangeable sodium were measured at the end of each phase of the study. Plasma renin concentration was measured by the method of Gould et al.

Studies were conducted with the patient in the supine position after 1 hour of bed rest. The study was approved by the Human Research Committee of the Hahnemann Medical College and Hospital, and written informed consent was obtained from each patient.

Table 2. Mean Values of Hemodynamic, Blood Volume, Exchangeable Sodium, Plasma Renin Concentration, and Body Weight of 10 Patients During Volume Expansion and Depletion

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<tr>
<th>Hemodynamic measurement</th>
<th>Pattern I</th>
<th></th>
<th></th>
<th>Pattern II</th>
<th></th>
<th></th>
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<td>Case 9</td>
<td>Case 10</td>
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<td>4.22</td>
<td>3.49</td>
<td>4.41</td>
<td>4.73</td>
<td>5.60</td>
<td>4.84</td>
<td>4.35</td>
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<tr>
<td></td>
<td>C₂</td>
<td>4.58</td>
<td>4.91</td>
<td>4.93</td>
<td>5.54</td>
<td>4.73</td>
<td>5.00</td>
<td>4.83</td>
<td>3.46</td>
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<td>64</td>
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<td>133</td>
<td>111</td>
<td>92</td>
<td>100</td>
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<tr>
<td></td>
<td>C₂</td>
<td>100</td>
<td>76</td>
<td>86</td>
<td>100</td>
<td>157</td>
<td>124</td>
<td>113</td>
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<tr>
<td></td>
<td>C₃</td>
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<td>101</td>
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<td>143</td>
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<tr>
<td></td>
<td>C₄</td>
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<td>—</td>
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<td>156</td>
<td>135</td>
<td>113</td>
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<tr>
<td></td>
<td>C₅</td>
<td>102</td>
<td>—</td>
<td>83</td>
<td>—</td>
<td>131</td>
<td>123</td>
<td>87</td>
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<td>1413</td>
<td>1496</td>
<td>1694</td>
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<td>1870</td>
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<td></td>
<td>C₅</td>
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<td>3026</td>
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<td>5160</td>
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<td></td>
<td>C₂</td>
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<td></td>
<td>C₃</td>
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<td></td>
<td>C₄</td>
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<td>5597</td>
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<td>—</td>
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<td>5174</td>
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<td>ENa (ml/kg)</td>
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<td></td>
<td>C₂</td>
<td>4295</td>
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<td>—</td>
<td>0.6</td>
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<td>Weight (kg)</td>
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<td>72.4</td>
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<td>65.9</td>
<td>66.1</td>
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</table>

C₁ = control phase (beginning of study); E = volume expansion phase; S = sustained volume expansion phase; D = volume depletion phase; C₂ = control phase (end of study); — = study was not performed; GU = Goldblatt unit; MAP = mean arterial pressure; TPRI = total peripheral resistance index; ENa = exchangeable sodium.
two patients during the sustained volume expansion phase increased by 7.0% and 22.4% of the controls respectively (table 2).

Pattern II

With progressive increase in body weight during salt- and water-loading, there was an increase in BP associated with an increase in cardiac output, both of which remained elevated throughout the phase of volume expansion. Conversely, with a decrease in body weight, the blood volume, BP, and cardiac output decreased toward control level. Total peripheral resistance did not show consistent changes (fig. 2). This pattern was observed in two patients with end-stage kidney disease (Cases 3 and 4). In Case 3, the average mean arterial pressure increased by 37 mm Hg above the control value during the sustained volume expansion phase; in Case 4, it increased by 22 mm Hg. Mean body weight and mean blood volume of these two patients during the sustained volume expansion phase increased by 7.6% and 23.5% respectively (table 2).

Pattern III

With progressive increase in body weight during salt- and water-loading, BP increased simultaneously with an increase in total peripheral resistance from the beginning. There were no significant changes in cardiac output. When the body weight decreased, the BP and peripheral resistance decreased. This pattern was
observed in two anephric patients (Cases 5 and 6) and three patients with end-stage kidneys (Cases 7, 8, 9), and is illustrated in figure 3. During the sustained volume expansion phase, the average MAP of these five patients increased by 25 ± 9 mm Hg (mean ± SD), while the mean body weight and mean blood volume increased by 7.1% ± 3.9% (mean ± SD) and 12.5% ± 2.5% (mean ± SD) respectively (table 2).

**Pattern IV**

In one anephric patient (Case 1), the progressive increase in body weight during salt- and water-loading was associated with an increase in BP and an initial increase in cardiac output followed later by an increase in total peripheral resistance. This patient had two steps of volume expansion: the first step occurred...
between Days 5 and 9 of the study, and the second between Days 10 and 12. During the first step, with a small increase in body weight (0.9 kg), there was an initial rise in cardiac output followed by an increase in BP and total peripheral resistance. During the second step, with a substantial increase in body weight (2.1 kg), there was a further increase in BP associated with an increase in cardiac output followed later by a further increase in total peripheral resistance (fig. 4).

During the sustained volume expansion phase, the average MAP increased by 62 mm Hg while the mean body weight and blood volume increased by 4.7% and 10.4% respectively (table 2).

**Relationship Between Blood Pressure, Blood Volume, and Total Exchangeable Sodium**

There was a significant positive correlation between BP and blood volume ($p < 0.01$) and between BP and
FIGURE 4. Case 10. Sequential hemodynamic changes during volume expansion. This patient had two steps of volume expansion: during the first step (volume expansion\textsubscript{1}), there was an initial rise in cardiac output followed by an increase in mean arterial pressure and total peripheral resistance. During the second step (volume expansion\textsubscript{2}), there was a further increase in mean arterial pressure associated with an increase in cardiac output followed later by a further increase in total peripheral resistance. The dashed lines indicate control values.

Peripheral Plasma Renin Concentration During Volume Change

Plasma renin concentration was determined in five of the six patients with end-stage kidneys and three of the four anephric patients. Control plasma renin concentrations of the five patients with end-stage kidneys were normal or low. No correlation between plasma renin concentration and volume changes was found. Plasma renin was not detectable in the three anephric patients studied (table 2).

Discussion

Introduction of the artificial kidney and arteriovenous shunt for maintenance hemodialysis in patients with end-stage renal disease has made it possible to perform sequential hemodynamic studies. Anephric patients and those with end-stage kidneys on maintenance hemodialysis have no renal excretory function, and their body fluids are controlled by their salt and fluid intake and by the amount of salt and water removed by the artificial kidney. Therefore, patients' body weights can be controlled by varying these parameters. Hemodynamic studies and sampling of blood can be performed noninvasively through an external connector inserted between the
arterial and venous side of the arteriovenous shunt used for hemodialysis.

In two patients, salt- and water-loading failed to significantly increase BP. Body weight (7.0% vs 6.9%) and blood volume (22.4% vs 15.3%) increased in the same proportion as in the eight patients in whom salt- and water-loading increased the BP. Thus, volume expansion per se does not invariably increase BP. In contrast to the remaining eight patients (the responders), these two nonresponders did not have a prior history of hypertension. The reasons for the difference between the responders and nonresponders are not clear. The following mechanisms, however, may be considered: 1) a genetic predisposition may play a role in this difference; 2) sodium chloride- and water-logging of the arteriolar wall is more conspicuous in the thickened arteriole of patients with previous hypertension; 3) structural changes in the arterioles induced by previous hypertension, similar to those described by Folkow, may determine vascular sensitivity to volume expansion in those patients with previous hypertension; 4) activity of the adrenergic nervous system may be more prominent in some patients.

In the remaining eight patients, salt- and water-loading resulted in a significant increase in BP; this increase, however, was accompanied by three different sequences of hemodynamic events. In two patients, the BP increase was associated with an increase in cardiac output only. Persistently high cardiac output was observed for a 3-week period during the volume expansion phase. This was not followed by an increase in total peripheral resistance. Thus, it would appear that the cardiac output was the major factor in increasing BP in these patients. In patients with end-stage renal disease subjected to a high sodium diet for 10 to 14 days, an increase in BP was associated with only an increase in cardiac output has been reported. Bravo and co-workers described a similar persistent increase in cardiac output in some dogs with hypertension induced by metyrapone. In our patients, it is evident that the secondary increase in total peripheral resistance predicted by the theory of whole-body autoregulation did not occur.

In five patients, the increase in BP was associated with an increase in total peripheral resistance from the beginning, without an initial increase in cardiac output. Thus, the increase in total peripheral resistance appears to be responsible for the increase in BP during the volume expansion phase. This resistance-mediated hypertension has been reported in metyrapone-induced hypertension in dogs, in two-kidney, two wrapped hypertension in rabbits, in hypertension induced by stimulation of stellate ganglion in dogs treated with propranolol, and in hypertension induced by deoxycorticosterone in pigs. Conway also reported that in one-kidney, one clip hypertension in the dog, the BP rise appears to be due entirely to an increase in peripheral resistance. The mechanism responsible for this primary increase in total peripheral resistance remains uncertain. The renin-angiotensin system could not play a role because two of the five patients studied were anephric and plasma renin was not detectable. Control plasma renin concentrations of the two patients with end-stage kidneys were low, and no correlations between plasma renin concentration and volume changes were found. It has been demonstrated by De Champlain and co-workers that sodium-loading facilitates sympathetic transmission and the release of norepinephrine from adrenergic granules. Thus, increased sympathetic activity may play a role in increasing total peripheral resistance during the salt-loading phase in our patients. Mark and associates also showed that excessive sodium intake for 10 days in patients with borderline hypertension increased BP, forearm vascular resistance, and neurogenic vasoconstriction. Sodium chloride- and water-logging of the arteriolar wall has also been considered a mechanism for increasing total peripheral resistance.

In one anephric patient during the volume expansion phase, cardiac output increased initially; this was followed by a progressive increase in BP and total peripheral resistance. A similar sequence of hemodynamic events has been described by Coleman and co-workers in three anephric patients. It has been postulated that the initial increase in cardiac output results in perfusion of the peripheral tissues above their metabolic needs. This would elicit myogenic constriction of peripheral vessels with consequent increase in total peripheral resistance.

As shown in tables 1 and 2, it appears that anephric patients do not respond to salt- and water-loading differently from patients with end-stage kidneys. In patients in whom salt- and water-loading elevated BP, there was a significant positive correlation between BP and blood volume and between BP and total exchangeable sodium. This is in accord with previous reports.

Despite equivalent degrees of body fluid expansion, hemodynamic responses to salt- and water-loading followed different patterns which are likely to reflect different mechanisms.

It is concluded that an initial rise in cardiac output is not necessary to increase BP and total peripheral resistance during salt- and water-loading in patients deprived of renal excretory function. Furthermore, a sustained rise in cardiac output during salt- and water-loading is not always followed by an increase in total peripheral resistance. Mechanisms other than whole-body autoregulation play a role.

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Sequential hemodynamic changes in end-stage renal disease and the anephric state during volume expansion.

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