Regulation of Arterial Pressure in the Anephric State

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SUMMARY

Three anephric patients were studied during sequential periods of normal hydration and overhydration. The increase in arterial pressure caused by the overhydration (+7% of body weight) was associated with an increase in peripheral resistance (+21.1%, \( P < 0.01 \)). The elevation of peripheral resistance was preceded by an increased cardiac output (+22.3%, \( P < 0.02 \)) which then fell part way to control levels (+13.2%, \( P < 0.05 \)). Return to normal hydration resulted in return of all variables to control levels. The fall in peripheral resistance was preceded by a transient fall in cardiac output to below control levels (−5.6%, not significant). With both normal and elevated pressures, plasma renin activity levels were low, and sensitivity to angiotensin infusion was greater than normal. Long-term autoregulation of blood flow is suggested as an important factor in the observed sequence of events.

Additional Indexing Words:

Hypertension Overhydration Cardiac output Peripheral resistance Long-term autoregulation

The anephric patient is special in that his fluid volume is no longer controlled by renal function but is dependent on the net difference between ingested and ultrafiltered water, not including insensible and fecal losses. This inadequacy of fluid volume control appears also to cause abnormal arterial pressure control, for hypertension during chronic hemodialysis is frequently associated with overhydration, and normal arterial pressures are frequently associated with optimal hydration. The following study was made in an attempt to clarify further these relationships.

Body fluid volumes were purposely altered by adjusting the rate of ultrafiltration for one or more periods of dialysis until a different level of hydration was reached. Basically, the study consisted of normal hydration followed by overhydration, followed again by normal hydration. Arterial pressure and cardiac output were measured, and peripheral resistance values were calculated from these measurements. Changes in circulatory function were correlated with changes in fluid volume.

Methods

This study was made on three bilaterally nephrectomized patients undergoing chronic hemodialysis, patients who also had chronically implanted A-V shunts of the Scribner type. Weight, arterial pressure, and cardiac output were determined preceding hemodialysis twice weekly. Table 1 gives a summary of patient data.

Intra-arterial pressure determinations were made by connecting part of the patient's shunt, a side-arm connector, to a Statham strain-gauge transducer and then momentarily stopping shunt flow by compressing the shunt distal to the side-arm connector. Cardiac output was measured by

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*Cat. 11-107, Cobe Laboratories, Denver, Colorado.
Table 1

Summary of Patient Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Optimum weight (kg)</th>
<th>Duration of study (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.C.</td>
<td>F</td>
<td>28</td>
<td>56</td>
<td>105</td>
</tr>
<tr>
<td>E.M.B.</td>
<td>F</td>
<td>5</td>
<td>13</td>
<td>25</td>
</tr>
<tr>
<td>I.L.</td>
<td>F</td>
<td>22</td>
<td>73</td>
<td>39</td>
</tr>
</tbody>
</table>

The dye-dilution technic using indocyanine green (Cardio-Green) dye. The dye (5 mg/ml in 0.5 or 1 ml aliquots) was injected into the venous end of the flowing shunt through a side-arm connector. Arterial blood was continuously withdrawn from another side-arm connector on the arterial end of the shunt through a Gilford Model 103 IR densitometer. Each cardiac output value was the average of triplicate determinations. The densitometer was calibrated by using a solution of 100 μl of stock dye mixed with 50 ml of blood. The blood was reinfused into the patient at the completion of the calibration procedure under sterile conditions. This technic has been described in detail elsewhere.1, 2 Permanent records were made on a model 1108 Visicorder.

Plasma renin activity and pressure response to angiotensin infusion were determined during periods of normal and elevated arterial pressure. Plasma renin activity was determined according to the method of Skinner3 and angiotensin infusion procedures were those of Kaplan and Silah.4

Results

Overhydration led to increased arterial pressure in each patient, and the rise in pressure was associated with a specific sequential pattern of cardiac output and peripheral resistance changes. Figure 1 shows the response of one patient to a sustained increase in body weight of approximately 4 kg or 5%. In terms of fluid volume this presumably was a change of 4 L. Mean arterial pressure rose from a control value of 98 mm Hg to a plateau value of approximately 137 mm Hg, an increase of nearly 40 mm Hg. Cardiac output increased over 2 L/min during the initial period of increased pressure and then decreased toward normal. Peripheral resistance increased from a control value of 0.017 mm Hg/ml/min to a plateau value of approximately 0.022 mm Hg/ml/min, an increase of nearly 30%. When the excess fluid volume was removed, arterial pressure, cardiac output, and peripheral resistance returned to normal. In the average data from the three patients, decreasing fluid volume and arterial pressure were accompanied by a fall in cardiac output to a value below control level, but this trend was not evident in the data of figure 1. Average data will be presented later.

Figure 2 shows the data of figure 1 replotted to show the relative contributions of cardiac output and total peripheral resistance in elevating arterial pressure as functions of time. The percentage changes were calculated with respect to average control values. The increased arterial pressure was initially caused by increased cardiac output. Peripheral resistance was in fact reduced during this period, but after approximately the 18th day of overhydration, elevated arterial pressure was then maintained primarily by increased peripheral resistance.

Figure 1
Arterial pressure, cardiac output, and peripheral resistance changes during body weight changes, that is, fluid volume changes, in one patient (I.L.).
Due to the dissimilar lengths of the observation periods, the data from the three patients were arbitrarily divided into five chronological periods and averaged. The results are shown in figure 3. Average values (mean ± standard error of the mean) and statistical significance (comparison with the control period) are summarized in table 2. Overhydration is divided into an initial period of increasing volume, a middle period of constant volume (plateau), and a final period of decreasing volume. The average duration of each period was as follows: first control period, 4 days; period of increasing volume, 10 days; period of constant volume, 11 days; period of decreasing volume, 22 days; and second control period, 10 days. It can be seen that mean arterial pressure was significantly elevated during the entire overhydration period. Cardiac output was highest (+22.3%) during the increasing volume period and was slightly but significantly elevated (+13.2%) during the plateau period. Cardiac output fell to below control (−5.6%, not significant) during the period decreasing volume. Peripheral resistance became significantly elevated (+21.1%) during the plateau period and remained elevated (+31.6%) during the period of decreasing volume.

The plasma renin activity data and angiotensin infusion data are summarized in table 3. Plasma renin activity was very low during periods of both normal and elevated arterial pressure. The pressor infusion rate of angiotensin, that is, the rate needed to produce a 20-mm Hg rise in diastolic arterial pressure, was below Kaplan and Silah's normal of 6 to 11 ng angiotensin/kg/min during both periods of normal and elevated pressure.

Table 2

<table>
<thead>
<tr>
<th>Statistical Significance of the Deviations from Control Values of Three Anephric Patients During Hydration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
</tr>
<tr>
<td>Cardiac output</td>
</tr>
<tr>
<td>Peripheral resistance</td>
</tr>
<tr>
<td>Weight</td>
</tr>
</tbody>
</table>

Abbreviation: NS = not significant.

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A limited number (six during control, 22 during overhydration) of chemical determinations on the serum was made before dialysis during this study as a part of regular hemodialysis procedures. Serum sodium averaged 140 mEq/L during control and 143 mEq/L during overhydration. Serum potassium averaged 4.4 mEq/L during control and 4.8 mEq/L during overhydration. Blood urea nitrogen averaged 91 during control and 86 mg/100 ml during overhydration. None of the changes were statistically significant.

**Discussion**

This study shows that chronic volume expansion in anephrics causes a reversible increase in arterial pressure that is a function of changes in both cardiac output and peripheral resistance. The initial elevation of arterial pressure in the patients studied was caused by an increase in cardiac output (+22.3%, \( P < 0.02 \)) and not by an increase in peripheral resistance (+3.0%, NS). Fluid volume was maintained as closely as possible at a constant increased level (+7.4% of body weight, \( P < 0.001 \)). During the plateau period increased peripheral resistance (+21.1%, \( P < 0.01 \)) replaced cardiac output (+13.2%, \( P < 0.05 \)) as the primary cause of the elevated pressure.

Aggressive ultrafiltration returned arterial pressure to normal. The period of decreasing fluid volume was characterized by a cardiac output that was decreased below control (−5.6%) but the change was not significant. Peripheral resistance during this period was the highest of any observed during the study.

![Figure 3](image)

**Cardiovascular response of three anephric patients to overhydration.**

<table>
<thead>
<tr>
<th>Normal arterial pressure</th>
<th>Elevated arterial pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma renin activity (units*)</td>
<td>Plasma renin activity (units*)</td>
</tr>
<tr>
<td>Normal values</td>
<td>50-80</td>
</tr>
<tr>
<td>Patient E.M.B.</td>
<td>0</td>
</tr>
<tr>
<td>I.L.</td>
<td>0</td>
</tr>
<tr>
<td>M.C.</td>
<td>0</td>
</tr>
<tr>
<td>Pressor dose of angiotensin (+20 mm Hg diastolic pressure) (units†)</td>
<td>Pressor dose of angiotensin (units†)</td>
</tr>
<tr>
<td>—</td>
<td>30</td>
</tr>
<tr>
<td>—</td>
<td>NA</td>
</tr>
<tr>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>—</td>
<td>4</td>
</tr>
<tr>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>—</td>
<td>4</td>
</tr>
</tbody>
</table>

* Nanograms angiotensin/1 ml plasma/4 hr incubation.
† Nanograms angiotensin/kg/min.
CONTROL OF BLOOD PRESSURE IN ANEPHRICS

(+ 31.6%, P < 0.02), higher even than the resistance observed during the period of maximum volume expansion.

The low plasma renin activity during both normal and elevated arterial pressure levels is consistent with an absence of renal mass. The increased sensitivity to angiotensin infusion during both normal and elevated pressures can best be interpreted as an exaggerated vascular response resulting from the decreased endogenous angiotensin levels which, in turn, are caused by the nearly zero plasma renin levels.

A possible explanation for the increase in peripheral resistance in the face of an incapacitated renin-angiotensin system involves autoregulation of blood flow and the interrelationship between changes in cardiac output and peripheral resistance in the following manner: The increased fluid volume causes increased cardiac output, which in turn increases the arterial pressure. The increased cardiac output represents overperfusion of the body's tissues and is theoretically dealt with by local vascular constriction in widespread areas of the body intended to decrease blood flow back toward normal. The increased resistance could result from either decreased average size of the vascular lumen or a decrease in the total number of "open" vessels. The increased peripheral resistance further increases arterial pressure. Also the increased resistance reduces venous return, thereby decreasing the cardiac output back toward the control values. A more detailed discussion of this theory and a mathematical analysis of the various interrelationships has been presented elsewhere.5, 6

The observed increase in cardiac output preceding the increase in peripheral resistance is consistent not only with the above-mentioned theory but with the results of several different animal experiments. Ledingham and Cohen7 found an elevated cardiac output in the early stages of Goldblatt hypertension, and more recently Ferrario and McCubbin8 observed this phenomenon in dogs made hypertensive with cellophane-induced perinephritis. In our laboratory a transient increase in cardiac output was observed when subtotally nephrectomized dogs were made hypertensive by salt loading.9 In all cases there was a delayed increase in peripheral resistance.

The interrelationship between pressure, flow, and resistance is probably modified by two additional mechanisms: the baroreceptors and the elastic properties of the vasculature. A baroreceptor mediated vasodilatation in response to increased arterial pressure superimposed onto the autoregulatory pressure could account for the observed lack of increase in peripheral resistance during the early stages of pressure elevation. Data from several different laboratories10-12 indicate that the baroreceptors adapt to increased arterial pressure within a few days; therefore, the baroreceptors probably had already adapted to the increased pressure during the plateau period of overhydration. It would logically follow that the increased resistance observed during the period of decreasing fluid volumes was caused by a vasoconstrictor response of an adapted baroreceptor system to a falling arterial pressure.

In addition to the contribution of the baroreceptor reflexes, peripheral resistance might be modified by the effect of increased pressure causing an immediate increase in lumen size due to the elastic properties of the vasculature. Likewise, the decreasing pressure occurring during the period of decreasing fluid volume could have caused an immediate decrease in lumen size contributing to the temporary elevation in peripheral resistance.

In conclusion, this study, as well as many others, has shown that the arterial pressure of the anephric patient is very sensitive to fluid volume changes. This sensitivity occurs in the absence of a functioning renin-angiotensin system and is characterized by secondary changes in peripheral resistance following initial changes in cardiac output.

References

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