HORMONAL RESPONSE TO VOLUME DEPLETION IN NON-NEPHRECTOMISED PATIENTS ON REGULAR HAEMODIALYSIS

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Summary

The hormonal response to volume depletion by isolated ultrafiltration has been studied in seven non-nephrectomised haemodialysis patients. The mean reduction in blood volume was 14%, and pulmonary artery wedge pressure reduction averaged 77%. No increments in heart rate were observed in any of the patients. Cardiac output decreased while systemic vascular resistance increased. Mean arterial blood pressure remained stable in all but two patients. Significant increments in plasma vasopressin concentration were only found during hypotensive episodes, while in the whole group no significant increase was found. Both plasma renin activity, plasma aldosterone and plasma cortisol increased significantly during isolated ultrafiltration. The moderate increase in systemic vascular resistance indicates that the peripheral sympathetic nervous system — at least partly — was functioning. It was, however, not correlated with changes in any of the measured hormones. Furthermore the adrenal and cardiac response appeared to be absent.

Introduction

The present investigation was undertaken to evaluate to what degree the hormonal systems, which are assumed to be major participants in the regulation of body fluid volume and blood pressure, respond in chronic haemodialysis patients during volume depletion.

Isolated ultrafiltration was chosen (i) because isotonic volume depletion was intended, to prevent hypotensive episodes [1], (ii) to reduce loss of catecholamines in the dialysate [2] and (iii) to obtain an exact measurement of the composition and volume of ultrafiltrate.
Material and Methods

Seven non-nephrectomised patients, six males and one female, all on regular dialysis treatment three times weekly using Gambro Lundia major-13.5 dialysers were investigated during 1–2 hours’ isolated ultrafiltration.

Plasma vasopressin concentration (PAVP), plasma renin activity (PRA) and plasma aldosterone concentration (PAC) were measured by radioimmunoassay techniques [3–5]. Plasma cortisol concentration (PCC) was measured by a competitive protein binding technique [6] and adrenaline (A), noradrenaline (NA) and dopamine (D) concentrations by a radioenzymatic method after separation by thin-layer chromatography. Plasma osmolality (pOsm) was determined by freezing point depression, sodium and potassium concentrations by flame photometry.

A Swan-Ganz® flow-directed catheter was first inserted via an antecubital vein by percutaneous technique. The patient was then connected to the dialyser without connecting it to dialysate. Pressures in the superior vena cava (CVP), pulmonary artery (PAMP) and pulmonary artery wedge pressure (PAWP) were measured with the Swan-Ganz catheter. Cardiac output (CO) was determined by a thermodilution technique [7] and expressed as cardiac index (CI). Blood volume was measured at the end of the procedure by a RISA-method (Volumetron®) and blood volumes were calculated by the changes of haematocrit in blood samples from the superior vena cava, assuming constant erythrocyte volume. Arterial blood pressure (BP) was measured with a mercury manometer and the mean arterial pressure (MAP) was calculated as diastolic BP + 1/3 pulse amplitude. The systemic vascular resistance index (SVRI) was calculated as (MAP-CVP)/CI.

After a 30 min resting period a 45 min control period started. Every 15 min, haemodynamic parameters were measured and simultaneous blood samples for hormone analysis were taken from the arterial line. Ultrafiltration was controlled by negative pressure (20–50mmHg) obtaining an initial loss of 300–500ml/15 min. A steady decrease in PAWP was intended and ultrafiltration rate was regulated according to this. Blood sampling and measurements of blood pressures and cardiac output were continued and ultrafiltrate sampled every 15 min.

Results

The mean loss of ultrafiltrate was 290ml/15 min ± 16 (SE). The mean decrements in blood volume are shown in Figure 1 which also demonstrates the induced changes in PAWP, CI, MAP, SVRI and heart rate. No changes in the heart rate were observed in any of the patients during the procedure. This indicates that the observed decrements in cardiac output were due to decreased stroke volume.

Table I shows that plasma levels of vasopressin, renin, aldosterone and noradrenaline were elevated. Figure 2 shows the induced changes in PAVP, PRA, PAC and PCC. Figure 3 gives the observed changes in catecholamine concentrations. In one patient a minor temporary increase occurred in pOsm followed by an increase in PAVP. In another patient a transitory decrease was found in pOsm—from 300 to 270mOsm/kg—without any concomitant decrease in PAVP. No other significant changes were observed in pOsm. Vasopressin was undetectable
Figure 1. Circulatory parameters in the control period and during isolated ultrafiltration, beginning after samples at 0 min were obtained. 'n' indicates number of patients. Means ± SE are shown.
Figure 2. Effect of isolated ultrafiltration on plasma vasopressin, renin activity, aldosterone and cortisol concentration. For further explanation see legend to Figure 1.
TABLE I. Plasma hormone levels in seven non-nephrectomised haemodialysis patients in the control period and in ten recumbent normal subjects. Means ± SE are shown. Means were compared by the unpaired t-test

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<tr>
<th></th>
<th>Uraemic patients</th>
<th>Normal subjects</th>
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<tbody>
<tr>
<td></td>
<td>control period</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 7</td>
<td>n = 10</td>
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<tr>
<td>Vasopressin</td>
<td>(pg/ml)</td>
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<tr>
<td></td>
<td>5.1 ± 0.6 +</td>
<td>2.7 ± 0.3</td>
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<tr>
<td>Renin activity</td>
<td>(ng/ml/h)</td>
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<tr>
<td></td>
<td>4.2 ± 1.2 +</td>
<td>0.7 ± 0.3</td>
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<tr>
<td>Aldosterone</td>
<td>(pg/ml)</td>
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<td></td>
<td>392 ± 111 +</td>
<td>120 ± 8.4</td>
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<tr>
<td>Cortisol</td>
<td>(µg/100ml)</td>
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<td></td>
<td>11.5 ± 1.7</td>
<td>13.4 ± 2.3</td>
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<tr>
<td>Adrenaline</td>
<td>(nmol/l)</td>
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<td></td>
<td>0.91 ± 0.19</td>
<td>0.52 ± 0.06</td>
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<tr>
<td>Noradrenaline</td>
<td>(nmol/l)</td>
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<td></td>
<td>3.57 ± 1.00+</td>
<td>1.48 ± 0.14</td>
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<tr>
<td>Dopamine</td>
<td>(nmol/l)</td>
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<td>1.42 ± 0.46</td>
<td>0.65 ± 0.14</td>
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+ = p < 0.05

<table>
<thead>
<tr>
<th>MEAN ± SE</th>
<th>CONTROL</th>
<th>ISOLATED ULTRAFILTRATION</th>
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<tbody>
<tr>
<td>n</td>
<td>7</td>
<td>7</td>
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![Graph showing plasma concentration of catecholamines](image)

Figure 3. Effect of isolated ultrafiltration on plasma concentration of catecholamines. For further explanation see legend to Figure 1
in the ultrafiltrate, while catecholamine concentrations were half to one third of those found in plasma. Plasma hormone levels during the control period and the ultrafiltration period were compared, and this is shown in Figure 4 as per cent changes in hormone concentration induced by the reduction in blood volume.

Figure 4. Effect of volume depletion by isolated ultrafiltration on plasma hormone levels in non-nephrectomised dialysis patients. p calculated by Wilcoxon’s signed ranked test for paired comparison

Despite elevated plasma levels of AVP and NA before volume reduction, neither were significantly stimulated by the reduction in PAWP (77% ± 6%, mean ± SE). In contrast to this PRA, PAC and PCC were significantly elevated during the ultrafiltration. The hypotensive episodes observed in two patients were followed by increments in PAVP and NA. The patient whose NA level increased by 88% experienced a severe episode of low blood pressure after 60 min ultrafiltration, but with no increase in heart rate. The other patients had no or minor increases in NA as shown in Figure 4. No significant relationship could be found between NA levels and PAWP in the control period (r = 0.67). On the other hand the patients with the most pronounced elevations in NA (6.2, 8.2 and 3.2nmol/l) also showed the highest initial PAWP values (26, 13 and 10mmHg respectively).
Discussion

The elevated PAVP levels in these haemodialysis patients are in accordance with other published observations [8]. But in this study no effect of a reduction in PAVP could be demonstrated. In contrast to this a significant increase in PAVP was elicited by decrements in blood pressure. This is contrary to current theories on PAVP regulation [9] but fits with a recent publication [10] questioning the importance of blood volume in PAVP regulation. The observed increments in PRA indicate that in all but one patient (Figure 4) the kidneys responded adequately to volume depletion. But there was a poor correlation between increments in PRA and PAC. This and the increase in PCC indicate that a diminished metabolic clearance rate by the liver may have influenced the increments in PAC and PCC [11]. Major increments in PCC were only observed during the hypotensive episodes in two of the patients.

The heart rate did not increase in any of the patients during volume depletion, while a moderate increase in systemic vascular resistance was found in all patients. The first of these findings indicates a missing sympathetic response, while the second indicates that the peripheral sympathetic nervous system still functions to a degree that prevents hypotension despite the induced decrease in cardiac output.

Acknowledgments

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References

4 Ølgaard, K and Ladefoged, J (1977) Ugeskr. Laeg., 139, 1590

Open Discussion

KOCH (Frankfurt) We performed studies similar to yours. In contrast to you in pure ultrafiltration we did see a significant increase in plasma noradrenaline together with a rise of peripheral resistance. Could you specify what was the average volume removed during your two hours of ultrafiltration?
HAMMER It was between two and three litres.

KOCH That is comparable with our studies. We removed three kilos in four hours. Was there anything specific about your patients as far as frequent hypotensive episodes are concerned?

HAMMER No, both of them were slightly hypertensive but received no medication at all for it.

BERGSTROM (Chairman) Would you like to elaborate on which factors are of importance for the increase in peripheral vascular resistance during ultrafiltration, considering that circulating vasoactive hormones seem to be of no importance?

HAMMER I think that this study has clearly shown that these patients have no cardiac sympathetic response. They have no increase in heart rate during volume depletion and they seem to have no adrenal sympathetic response and actually the absolute increase in peripheral resistance is only moderate but it seems to indicate that the peripheral sympathetic nervous system still functions but not to a normal degree as we would have expected.

BERGSTROM It functions enough, in other words.

HAMMER Well, yes. I say that because two of the patients actually had sudden drops in blood pressure with a sudden decrease in peripheral resistance.

BERGSTROM Do you happen to have any control population, of non-uraemic patients, for instance, who are volume depleted to the same extent.

HAMMER No, not to the same extent.

RAMPL (Berlin) How did you begin the dialysis procedure. Did you start with or without the priming volume of the dialyser; and was your dialyser priming volume high or low?

HAMMER It was a Gambro LUNDIA Major.

RAMPL And you started without a priming volume?

HAMMER With a priming volume. The dialyser blood compartment was filled with saline.

RAMPL You have shown us very strong decrease in pulmonary artery pressure and you must think about the very high priming volume in this dialyser and a very high compliance too. So you can have an accidental drop of the pulmonary artery pressure combined with a very strong drop in the cardiac output and the stroke volume too. This is a very dangerous situation for the patient.

HAMMER That was why we had a 45 minute control period in each patient and it was completely stable for most parameters.

SMITH (Portsmouth) Can we always assume that the levels of adrenaline and
noradrenaline as measured in the plasma are a reflection of the activity of the
sympathetic nervous system, or in any of your patients did you actually infuse
noradrenaline or isoprenaline or atropine and see whether there was any heart
rate response or blood pressure response?

HAMMER No, I don’t think that the plasma can confidently reflect activity of
the peripheral sympathetic nervous system but it indicates whether the adrenal
response is still present.