The Influence of Volume Depletion and Central Hypovolemia on the Plasma Concentration of Parathyroid Hormone in Dialysis Patients

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Abstract. Because changes in extracellular volume during dialysis cause reflex neurohormonal changes that may influence parathyroid hormone (PTH) release independently of calcium, the influence of isotonic volume depletion (by isolated ultrafiltration) and central hypovolemia (70° tilt) on serum PTH was studied in 16 hemodialysis patients. Tilting was performed in volume depleted state, i.e., immediately after hemodialysis. In the control study, patients underwent sham ultrafiltration (UF = 0) and after dialysis maintained the supine position for the same length of time they remained in the tilt position in the active experiment. Isolated ultrafiltration (−2.3 ± SEM 0.3 L) caused a 21% fall in mean arterial pressure (from 101 ± 6 to 80 ± 6 mmHg, P < 0.01), a fall that was accompanied by a marked increase in plasma catecholamine levels (norepinephrine P < 0.001, epinephrine P < 0.025), in plasma renin activity (P < 0.001) and in plasma arginine vasopressin (P < 0.001). Atrial natriuretic factor showed a slight reduction, whereas the plasma endothelin-1 level did not change. Serum Ca showed the expected, hemoconcentration-dependent rise (from 4.1 ± 0.1 to 4.4 ± 0.1 meq/L, P < 0.01). Interestingly, UF caused a marked rise in plasma PTH1−84 concentration (from 252 ± 62 to 335 ± 72 pg/ml, P < 0.01). UF-induced changes in serum PTH1−84 were related to norepinephrine changes (r = 0.57) as well as to plasma renin activity (r = 0.50). After hemodialysis, tilting induced a pronounced rise in serum PTH1−84 (from 102 ± 29 to 200 ± 55 pg/ml), and these changes were slightly related to plasma epinephrine (r = 0.49) but independent of other parameters. In the control experiment, neither sham UF nor recumbency modified serum PTH. In hemodialysis patients, serum PTH is sensitive to changes in extracellular and central blood volume of magnitude sufficient to decrease arterial pressure. Avoiding marked volume stimuli might help to refine the interpretation of the Ca/PTH curves during hemodialysis in these patients. (J Am Soc Nephrol 8: 1574−1578, 1997)

Changes in serum calcium brought about by dialysate calcium content are undoubtedly the main factor regulating serum parathyroid hormone (PTH) during hemodialysis. However, extracellular fluid volume subtraction during dialysis activates several neurohumoral responses, including the stimulation of the adrenergic and the renin-angiotensin systems and of antidiuretic hormone (ADH) and endothelin (1). Because most of these factors, namely epinephrine and norepinephrine (2), angiotensin II (3), and endothelin-1 (4), in theory may also promote the release of PTH, we investigated whether extracellular volume depletion and central hypovolemia have an effect independent of serum calcium on plasma PTH concentration in dialysis patients.

Materials and Methods

Patients

Sixteen unselected uremic patients (ten male, six female; mean age, 48 ± 14 SD) on regular dialysis treatment participated in the study. They had been on treatment for periods ranging from 3 months to 19 years with cuprophan dialyzers (surface area ranging from 1.00 to 2.00 m2) manufactured by Gambro (Parma, Italy), Bellco (Miranda, Italy), and Organon (Akzo, Italy). The average Kt/V in these patients was 1.34 (range, 1.0 to 2.0). The cause of renal failure was polycystic renal disease in four, chronic glomerulonephritis in five, chronic pyelonephritis in two, cortical necrosis in one, and undefined in four patients. All were being dialyzed by cuprophan filters, using a standard dialysate (Na, 145 mmol/L; K, 1.5 mmol/L; HCO3, 37 mmol/L; Ca, 1.50 to 1.75 mmol/L; Mg, 0.5 mmol/L). Eight patients had a variable degree of left ventricular hypertrophy on echocardiography, but none had evidence of heart failure.

Study Protocol

The protocol of the study conformed with the ethical guidelines of our institution, and informed consent was obtained from each participant. Both the active and control experiments (see below) were performed midweek, after a short dialysis interval.

Active experiment. On the day of the study, each patient's blood pressure and heart rate were monitored at 3-min intervals for 30 min while they rested in a supine position on a dialysis bed equipped with a scale. Baseline blood sampling was performed at the end of this period. Isolated ultrafiltration (5) was then initiated at a rate of approximately 20 ml/min, and the ultrafiltrate was collected in a graduated cylinder. The procedure was interrupted when all of the body weight excess accumulated in the preceding dialysis interval was
removed. Blood sampling was again performed at midultrafiltration and at the end of ultrafiltration. Arterial pressure and heart rate were measured three times at a 3-min interval before sampling. Isovolumic dialysis (with a standard dialysate containing 1.75 mmol/l of calcium [see above]) was initiated. During isovolumic dialysis, the blood flow rate ranged from 180 to 350 ml/min and the dialysate flow rate was 500 ml/min. Arterial pressure and heart rate were monitored as during dialysis (with a standard dialysate containing 1.75 mmol/l of calcium removed. Blood sampling was again performed at midultrafiltration and at the end of ultrafiltration. Arterial pressure and heart rate were measured every 2 min while the final blood sample was taken, either after 30 min or—if signs of intolerance to the maneuver had supervened—immediately before returning the patient to the supine position.

Control experiment. In the control experiment, the inlet and the outlet of the dialyse compartment were accurately sealed to avoid ultrafiltration while the blood circulated through the filter (sham ultrafiltration). After sham ultrafiltration (which, in each case, lasted exactly as long as isolated ultrafiltration in the active experiment), isovolumic dialysis was carried out for 180 min as in the active experiment. At the end of dialysis, patients remained in bed in a supine position for the same length of time they had been in tilting position in the active experiment. Blood sampling for plasma PTH and serum Ca, phosphate, and protein concentration was performed at the same time points of the active experiment. Ten of 16 patients accepted to participate in the control experiment, which was performed 1 to 3 months after the active experiment. The six patients excluded from this part of the study were of similar age (48 ± 13 versus 52 ± 14 yr; not statistically significant [NS]), mean arterial pressure (107 ± 23 versus 97 ± 22 mmHg, NS), and plasma PTH (218 ± 125 versus 271 ± 70 pg/ml, NS) in comparison to the other ten patients.

Methods

Plasma PTH_1-84 level was measured by the Allegro kit (Nichols, San Juan Capistrano, CA). Plasma catecholamine levels and plasma renin activity (PRA) were measured by commercially available RIA methods (Amicly-test™, Immuno logical Laboratories, Hamburg, Germany and Rentck, Sorin, Vercelli, Italy). Atrial natriuretic factor (ANF) and endothelin-1 were measured on preextracted plasma samples according to methods established in our laboratory (6,7). Calcium, phosphate, and protein concentrations were measured by standard methods in the routine clinical laboratory of our institution. Arterial pressure and heart rate measurements were performed by an automatic sphygmomanometer connected to an automatic recorder (Dinamap, model 1540; Critikon, Tampa, FL).

Statistical Analysis

Baseline arterial pressure and heart rate represent the average value of the last three measurements recorded during supine rest periods. During isolated ultrafiltration and isovolumic dialysis, the average value of the three blood pressure and heart rate recordings before each blood sampling were considered. During tilt, the measurement was taken immediately before sampling.

Data are presented as mean ± SEM. Comparisons were performed by repeated-measures analysis of variance, followed by a multiple paired r test (UF and isovolumic dialysis data) and by the paired r test (tilt data) (8). Furthermore, in the ten patients who participated in both experiments (active and control), PTH changes induced by UF and by tilt were compared by the paired r test. The Pearson correlation coefficient was used to assess the degree of within-subject linear correlation between parameters of interest. Data were log-transformed before calculation when a tendency for sample variability to increase as the mean for a given response variable increased (9).

Results

Active Experiment

Isolated ultrafiltration (UF). The volume of ultrafiltrate removed during this procedure ranged from 0.2 to 3.5 L (average, 2.3 ± 0.2 L). As expected, isolated UF caused a significant increase in plasma proteins concentration (P < 0.01), which was strictly related with the ultrafiltrate volume (r = 0.81, P < 0.01). As shown in Table 1, mean arterial pressure fell significantly during UF, whereas heart rate showed a small rise (NS). As expected, UF caused a significant, hormone-dependent rise in serum protein and calcium levels, whereas serum phosphate levels did not change. PRA, ADH, and plasma catecholamine levels rose significantly, whereas ANF showed an opposite trend. Plasma endothelin was little affected by UF. As shown in Table 1 and in Figure 1 (left panel), plasma PTH_1-84 concentration showed a consistent rise after UF (from 252 ± 62 to 335 ± 73 pg/ml, P < 0.01), the average increase being 54% (range, 3% to 127%). Changes in plasma PTH were related to (log-transformed) norepinephrine changes (r = 0.57, P = 0.02) as well as to (log-transformed) PRA (r = 0.50, P = 0.04) but independent of plasma proteins concentration changes (r = 0.23, P = 0.394), UF volume, arterial pressure, epinephrine, and endothelin.

Isovolumic dialysis. During isovolumic dialysis, body weight did not change, and arterial pressure and heart rate showed a small rise (NS), whereas plasma norepinephrine and epinephrine reapproached baseline levels. PRA, ADH, and endothelin did not change, whereas ANF showed a further decline. As expected, serum calcium rose to 4.9 ± 0.1 mmol/l and serum phosphate fell to 1.18 ± 0.13 mmol/L, whereas PTH decreased to 102 ± 29 pg/ml (P < 0.01).

Tilt. Only three patients were able to maintain the tilt position for 30 min. The average tilt tolerance was 11.5 ± 2.7 min. Tilt caused a 8 mmHg fall in MAP associated with a significant rise in heart rate and in plasma catecholamine levels (Table 1). PRA, plasma endothelin, and plasma ANF, as well as serum Ca and phosphate levels, were unaffected by tilt. PTH showed a marked rise (from 102 ± 29 to 200 ± 55 pg/ml), the average increase being 100% (range, 17% to 322%) (Figure 1, right panel). Tilt-induced PTH changes were slightly related to changes in plasma epinephrine (r = 0.49, P = 0.05) but unrelated to arterial pressure, norepinephrine, PRA, and endothelin, as well as to the duration of tilt.

Control experiment

As shown in Table 2, serum Ca and phosphate levels, as well as plasma PTH levels, remained the same after sham UF. PTH changes after sham UF were significantly less than after isolated UF (P < 0.01). After isovolumic dialysis, the serum Ca level was lower than in the active experiment, whereas serum phosphate and plasma PTH were very similar to those observed in the active experiment. Bed-resting (for a period identical to that spent in the tilt position in the active experiment) after isovolumic dialysis did not change serum Ca and serum phos-
This study shows that extracellular volume depletion and superimposed central hypovolemia influence plasma PTH concentration in dialysis patients to an important extent.

Changes in serum calcium levels in the pathophysiological range induce well-defined variations in serum intact PTH in uremic patients on chronic hemodialysis, and elegant studies (10,11) have now clearly established that detailed analysis of this relationship (the PTH/Ca curve) gives important information for the study of parathyroid disorders in these patients.

Besides calcium, various factors may influence PTH secretion (2-4,12). Interestingly, at least two of these mechanisms, the adrenergic system and angiotensin II, represent key factors in cardiovascular homeostasis because both systems are markedly activated when the circulating volume is reduced. Indeed, it has been shown that beta-adrenergic stimulation with either nor-epinephrine or epinephrine increases PTH secretion in humans, an effect that is inhibited by propranolol (2). By the same token, angiotensin II infusion at a rate that will bring the plasma concentration of this peptide into the pathophysiological range produces a well-defined increase in plasma PTH concentration (3). Furthermore, there is in vitro evidence that endothelin-1, which may participate in the reflex response to central hypovolemia (13), may also influence PTH release (4).

The clear-cut rise in plasma PTH observed in this study shows that acute changes in extracellular volume and in central blood volume may have important effects on plasma PTH in dialysis patients. We have documented that this phenomenon is specifically linked to volume stimuli because in the control experiment no change in the plasma concentration of the hormone occurred either during sham ultrafiltration or during recumbency. In theory, the increase in plasma PTH after isolated UF could be purely caused by hemoconcentration. However, the correlation coefficient of the relationship between PTH and plasma protein changes was low (r = 0.23), indicating that at most, only 5.3% (r² = 0.053) could be attributed to this factor. The increased plasma PTH concentration may depend on an enhanced secretion rate or reduced degradation of the hormone. Once released, PTH is rapidly metabolized in the liver (14). In theory, hypovolemia could have induced a baroreflex-mediated vasoconstriction in the liver, and the ensuing decrease in liver blood flow could have reduced the metabolic clearance of PTH. Although the issue remains un-

Table I. Hemodynamic and metabolic measurements in the active experiment†

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Mid-UF</th>
<th>End-UF</th>
<th>Mid-HD (Isovolumic)</th>
<th>End-HD (Isovolumic)</th>
<th>Tilt</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>101 ± 6</td>
<td>94 ± 6</td>
<td>80 ± 6b</td>
<td>84 ± 6</td>
<td>83 ± 5</td>
<td>75 ± 6</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>76 ± 2</td>
<td>77 ± 3</td>
<td>81 ± 3</td>
<td>84 ± 3</td>
<td>89 ± 3</td>
<td>105 ± 4c</td>
</tr>
<tr>
<td>Total proteins (g/dl)</td>
<td>6.6 ± 0.2</td>
<td>8.2 ± 0.3b</td>
<td>8.6 ± 0.3b</td>
<td>8.1 ± 0.3</td>
<td>7.9 ± 0.3</td>
<td>8.0 ± 0.2</td>
</tr>
<tr>
<td>Ca (meq/L)</td>
<td>4.1 ± 0.1</td>
<td>4.4 ± 0.1b</td>
<td>4.5 ± 0.1b</td>
<td>4.8 ± 0.1d</td>
<td>4.9 ± 0.1d</td>
<td>4.9 ± 0.1</td>
</tr>
<tr>
<td>Phosphate (mmol/L)</td>
<td>1.84 ± 0.11</td>
<td>1.83 ± 0.11</td>
<td>1.88 ± 0.13</td>
<td>1.26 ± 0.11d</td>
<td>1.18 ± 0.13d</td>
<td>1.16 ± 0.13</td>
</tr>
<tr>
<td>PRA (ng/ml/per h)</td>
<td>5.1 ± 1.4</td>
<td>12.7 ± 4.6b</td>
<td>16.0 ± 6.1b</td>
<td>16.6 ± 7.4</td>
<td>18.0 ± 7.0</td>
<td>19.1 ± 7.3</td>
</tr>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>327 ± 33</td>
<td>607 ± 50b</td>
<td>785 ± 84b</td>
<td>487 ± 53d</td>
<td>504 ± 66d</td>
<td>508 ± 109c</td>
</tr>
<tr>
<td>Epinephrine (pg/ml)</td>
<td>25 ± 4</td>
<td>38 ± 6</td>
<td>67 ± 16a</td>
<td>35 ± 16d</td>
<td>42 ± 9d</td>
<td>90 ± 19c</td>
</tr>
<tr>
<td>ANF (pg/ml)</td>
<td>90 ± 12</td>
<td>83 ± 11</td>
<td>84 ± 11</td>
<td>64 ± 8</td>
<td>76 ± 8</td>
<td>81 ± 6c</td>
</tr>
<tr>
<td>ADH (pg/ml)</td>
<td>3.4 ± 0.3</td>
<td>4.3 ± 0.4</td>
<td>14.1 ± 4.1b</td>
<td>5.2 ± 0.8d</td>
<td>7.7 ± 2.3d</td>
<td>18.9 ± 5.1c</td>
</tr>
<tr>
<td>Endothelin (pg/ml)</td>
<td>17.1 ± 1.2</td>
<td>18.8 ± 1.6</td>
<td>18.5 ± 1.6</td>
<td>16.8 ± 1.2</td>
<td>18.7 ± 1.9</td>
<td>17.9 ± 1.5</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>252 ± 62</td>
<td>299 ± 75b</td>
<td>335 ± 73b</td>
<td>117 ± 32d</td>
<td>102 ± 29d</td>
<td>200 ± 55c</td>
</tr>
</tbody>
</table>

* UF, ultrafiltration; HD, hemodialysis; MAP, mean arterial pressure; PRA, plasma renin activity; ANF, atrial natriuretic factor; ADH, antidiuretic hormone; PTH, parathyroid hormone. Data are shown as mean ± SEM.

b P < 0.01 versus baseline.

c P < 0.01 versus end-HD.
d P < 0.01 versus end-UF.

© P < 0.025 versus baseline.

Figure 1. Changes in plasma PTH concentration induced by isolated ultrafiltration (left panel) and by tilt (right panel).
resolved, the fact that the rise in PTH caused by ultrafiltration and by tilt was unrelated to the ultrafiltration volume and to arterial pressure changes (a measure of the strength of the reflex hemodynamic stimulus imposed on the hepatic circulation) as well as to the duration of tilt, suggests that a reduced metabolic clearance is unlikely to represent the primary factor responsible for the PTH changes induced by these volume stimuli. The slight correlations between PTH, plasma catecholamines, and PRA are in line with the known effects of these factors on the parathyroid gland, but it remains to be seen if these correlations entail causal links, i.e., that these factors directly enhance PTH release, or if they represent mere associations. Hypotension and intravascular volume depletion might compromise tissue perfusion and by this mechanism induce some degree of acidosis. If so, acidosis could have raised ionized calcium, thereby attenuating the PTH rise elicited by volume depletion. It is interesting to note that in a previous study Heintz et al. (15) observed a 47% rise in serum PTH level during standard dialysis in patients with dialysis hypotension but no such change in patients with stable arterial pressure. On this basis he speculated that PTH may play a role in hemodynamic instability during dialysis. PTH has vasodilatory properties in vitro and in vivo in various animal species (16). Such properties become evident in humans only when the hormone is administered in pharmacological doses (17). However, it has been argued that some of the effects of PTH on the cardiovascular system, such as the inhibition of L-type Ca channels, may occur at physiological concentrations in vivo (18) and that in uremic subjects, raised PTH levels may counteract the vasoconstrictor effect of norepinephrine (19). In our study, the arterial pressure response to extracellular volume depletion and central hypovolemia was largely independent of ongoing changes in plasma PTH concentration.

Perhaps the main implication of our study is that volume stimuli, although contributing much less than calcium in the regulation of plasma PTH, cannot be overlooked in studies aimed at defining the Ca/PTH curve in dialysis patients. These curves are constructed using data collected by sequentially dialyzing the patients with a low- and a high-calcium dialysate (8). It has been argued that small errors in the measurement of PTH or ionized calcium may produce substantial variation in the slope estimate of the Ca/PTH curve (20). In studies evaluating treatment-induced changes in parathyroid function or comparing groups of dialysis patients with different parathyroid disorders, the comparison of such curves might be disturbed if experimental data are unmatched for fluid removal. Such a possibility has to be tested in a specifically designed study. Furthermore, it remains to be seen whether the effect of volume stimuli on plasma PTH is additive to that of hypocalcemia.

Table II. Control study*

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Sham-UF</th>
<th>End-HD (isovolumic)</th>
<th>Recumbency</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>97 ± 5</td>
<td>90 ± 6</td>
<td>91 ± 5</td>
<td>93 ± 5</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>75 ± 4</td>
<td>73 ± 4</td>
<td>86 ± 4*</td>
<td>85 ± 3</td>
</tr>
<tr>
<td>Total proteins (g/dl)</td>
<td>6.5 ± 0.2</td>
<td>6.4 ± 0.3</td>
<td>6.3 ± 0.2</td>
<td>6.3 ± 0.3</td>
</tr>
<tr>
<td>Ca (meq/L)</td>
<td>4.5 ± 0.2</td>
<td>4.4 ± 0.2</td>
<td>4.6 ± 0.2</td>
<td>4.6 ± 0.2</td>
</tr>
<tr>
<td>Phosphate (mmol/L)</td>
<td>1.88 ± 0.21</td>
<td>1.84 ± 0.21</td>
<td>1.01 ± 0.23*</td>
<td>1.21 ± 0.07</td>
</tr>
<tr>
<td>PTH1-84 (pg/ml)</td>
<td>245 ± 70</td>
<td>243 ± 86</td>
<td>120 ± 36*</td>
<td>157 ± 44</td>
</tr>
</tbody>
</table>

* In this study patients underwent sham ultrafiltration followed by isovolumic hemodialysis and then remained supine in the dialysis bed for a period identical to that of the tilt study (see the Methods section). Data are mean ± SEM.

References