Volume sensitivity of blood pressure in end-stage renal disease

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Abstract

Background. The influence of interdialysis (ID) volume expansion on the blood pressure (BP) change and on the BP level at the end of the ID time period was studied in 167 chronic haemodialysis patients. Our analysis focused on 120 patients not receiving antihypertensive drugs (untreated group). The remaining 47 patients were receiving antihypertensive medication (treated group).

Methods. The ID weight gain was considered equivalent to the volume gain. In each patient the mean ID BP change (as percent change of initial BP) and the mean ID volume expansion related to the lean body mass (ml.kg⁻¹) were determined from 25 consecutive ID time periods. The individual volume sensitivity of BP was expressed as the BP change divided by the volume expansion. Basal overhydration was estimated as mean ID initial weight minus dry weight.

Results. All patients gained volume during ID time periods and the BP was increased in 91%. The change of mean BP (MBP) was directly correlated with volume expansion (r=0.45, P<0.00001) only in the untreated group. These patients showed a volume sensitivity unrelated with age, serum urea and calcium concentrations and haematocrit. Sensitivity of diastolic BP (DBP), an indicator of the capacity to respond to volume expansion by vasoconstriction (autoregulatory process), exhibited a negative correlation with the initial DBP level (r = -0.36, P<0.0001) and with the serum potassium (in women, r = -0.35, p < 0.02). These factors appeared to counteract the volume-induced DBP response. The MBP levels at the end of ID time periods were independent of volume expansion and basal overhydration. Hypertensive patients showed a higher sensitivity than normotensive patients (0.35 ± 0.2 versus 0.20 ± 0.19% per ml.kg⁻¹, P<0.005). Final MBP showed a positive correlation with initial MBP and, to a smaller extent, with serum urea concentration.

Conclusions. In our study the ID change of BP is partially dependent on volume gain. Volume sensitivity is a measure of the BP responsiveness and is higher in hypertensive patients. Final BP depends on the height of initial BP and other factors accounting for volume sensitivity, whose precise nature remain to be clarified.

Key words: hypertension; interdialysis time period; sensitivity of blood pressure; uraemia; volume expansion

Introduction

Chronic overhydration is a cause of high BP in end-stage renal disease [1]. Removal of salt and water by diuretics or dialysis frequently improves or normalizes uraemic hypertension [2–4]. In chronic renal failure, a significant positive correlation exists between plasma volume and BP [5]. Koomans et al. [6] demonstrated that the increase in extracellular volume induced by sodium loads correlates positively with increments in BP.

Interdialysis time periods are associated with fluid overload and are useful for the study of the changes in BP associated with volume gain. Contrary to expectations, no association between interdialysis weight gain (a measure of total body fluid expansion) and BP change [7–9] or the value of predialysis BP [10] has been apparent.

In the present study we examine the possible influences of volume on BP during the interdialysis time period, attempting a quantitative analysis of the effects of volume expansion on the change in BP and on final BP level.

Subjects and methods

We studied 167 adult uraemic patients (male 106, female 61) on maintenance haemodialysis in five centres in Montevideo, Uruguay. Patients included in the study had been on dialysis for more than 6 months (range 8–82) and were divided in two groups: patients not receiving antihypertensive medication or drugs affecting BP at entry and during the study period of 60 days (untreated group, n = 120) and patients receiving antihypertensive drugs who served as a comparative group (n = 47). Patient data are given in Table 1. The estimated ‘dry’ weight (lowest postdialysis weight regularly attained without hypotension) was used for the calculation.
of the lean body mass (LBM) according to the formulae:

Men LBM = 0.407 × weight + 26.7 × height – 19.2

Women LBM = 0.252 × weight + 47.3 × height – 48.3

These formulae are based on the regression formulae for calculating total body water (TBW) [11]. They are based on the relationship TBW = 0.73 LBM [12] and have been used for estimating LBM in patients with chronic renal failure [6].

Predialysis serum urea, potassium and calcium concentrations and haematocrit values were measured three times over the study period and the values were averaged.

Both groups of patients were comparable in terms of primary renal diagnoses and dialysis schedules. Clinical and/or histological diagnoses of underlying nephropathies were arteriolar nephrosclerosis (16% of patients), chronic glomerulonephritis (27%), diabetic nephropathy (7%), tubulointerstitial nephropathy (24%), polycystic kidney disease (10%), and unknown (16%). Nine patients had undergone subtotal nephrectomy and one was anephric. Thrice-weekly dialysis (12–14 h/week), with cuprophane dialysis membranes, demineralized water, and acetate (93% of patients) or bicarbonate (7% of patients) buffer, were performed. Sodium concentration of the dialysate was 140 mmol/l. Six patients received recombinant human erythropoietin (rHuEpo) and 11 received androgens for the treatment of the anaemia.

Blood pressure was taken 30 min after the end of the dialysis session (value considered as the initial interdialysis BP), and before the start of the subsequent dialysis session (final interdialysis BP). Patients were seated, at rest, mercury sphygmomanometers and appropriate cuff sizes were used by trained nursing staff. Disappearance of bruits (Korotkoff phase V) identified diastolic BP (DBP). Mean BP (MBP) was calculated as DBP + 1/3 pulse pressure. Body weight of barefoot patients in underclothes was measured with a beam scale and under identical conditions on successive records.

**Interdialysis time period**

Every patient was evaluated for 25 consecutive interdialysis time periods. Interdialysis periods lasted from 44 to 68 h. The difference between the average initial and final interdialysis values of BP was expressed as the individual mean change of BP. The interdialysis body weight was calculated in the same fashion.

Blood pressure change was expressed as percentage of initial pressure. Weight gain was considered to reflect total fluid volume expansion (1 kg = 1000 ml). The changes in volume were corrected for LBM (ml per kg of LBM) to obtain comparable values of volume load between individuals and to take into account the fact that body mass is strongly and independently related to BP [13]. The BP change divided by the volume gain in each patient was defined as the individual volume sensitivity of BP.

This sensitivity index was calculated for systolic BP (SBP), DBP and MBP. A rough estimate of the basal overhydration during the study period was calculated as the mean initial weight minus the dry weight. Patients whose final level of MBP exceeded 107 mmHg (140/90 mmHg) were classified as hypertensive.

**Statistical analysis**

Simple regression and multiple linear regression analyses with analysis of variance (ANOVA) were carried out to compare interdialysis BP changes or final BP levels with volume expansion, initial BP, age, serum urea, calcium and potassium and haematocrit. Changes within groups were compared using Student’s t test for paired data, and differences between the groups with unpaired Student’s t test. Results were expressed as mean ± SD. The null hypothesis was rejected when \( P < 0.05 \).

**Results**

The untreated group and the group receiving antihypertensive medications were comparable in terms of basal overhydration, interdialysis weight gain and MBP increase (Table 2). All patients increased body weight (range 0.4–4.2 kg). MBP increased in 91% of patients of the untreated group (range of blood pressure changes, -7 to 31%) and in 94% of treated patients (range of BP changes, -3 to 22%). The MBP levels at the beginning and the end of the interdialysis time period were higher in the treated group.

There was a highly significant, positive correlation between interdialysis increase of MBP and weight gain in the untreated group \( (r = 0.47, P < 0.00001) \). No such correlation was found in patients receiving antihypertensive therapy (Figure 1). Likewise, the increment in MBP was correlated with the expansion of volume corrected for LBM in the group of 120 untreated patients \( (r = 0.45, P < 0.00001) \), but not in treated patients \( (P = NS) \). Analyses were therefore pursued only in the untreated population.

There were marked differences among individuals with respect to the degree of BP response to each increment in volume, indicating variable sensitivity to volume load. Calculated sensitivity of MBP had a near

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Sex (% men)</th>
<th>Lean body mass (kg)</th>
<th>Serum levels (mmol/l)</th>
<th>Urea</th>
<th>Potassium</th>
<th>Calcium</th>
<th>Haematocrit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>59 ± 16</td>
<td>63</td>
<td>50 ± 9</td>
<td>23.3 ± 4</td>
<td>5.4 ± 0.5</td>
<td>2.2 ± 0.2</td>
<td>26 ± 5</td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>55 ± 15</td>
<td>66</td>
<td>50 ± 8</td>
<td>24.9 ± 4*</td>
<td>5.4 ± 0.6</td>
<td>2.3 ± 0.2</td>
<td>25 ± 5</td>
<td></td>
</tr>
</tbody>
</table>

\* \( P < 0.05 \).
Table 2. Interdialysis values of body weight and mean blood pressure (MBP) in the two groups of patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Basal overhydration* (l)</th>
<th>Weight gain (kg)</th>
<th>Initial MBP (mmHg)</th>
<th>Final MBP (mmHg)</th>
<th>Gain in MBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>1.1 ± 1.1</td>
<td>1.8 ± 0.7</td>
<td>89 ± 12</td>
<td>95 ± 12</td>
<td>8 ± 7</td>
</tr>
<tr>
<td>(n = 120)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>1.5 ± 1.7</td>
<td>2 ± 0.7</td>
<td>97 ± 9**</td>
<td>105 ± 9**</td>
<td>9 ± 7</td>
</tr>
<tr>
<td>(n = 47)</td>
<td></td>
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</tbody>
</table>

*Mean interdialysis initial weight minus estimated ‘dry’ weight, 1 kg = 1 l.
**P < 0.0005.

Fig. 1. Scatterplots showing relationships between percentage changes of MBP and weight gain or volume expansion per kilogram of lean body mass during interdialysis time periods. Symbols represent patients. A highly significant correlation was observed in patients not receiving antihypertensive medication (untreated group).

Fig. 2. Scatterplots showing relationships between percentage changes of MBP and volume expansion per kilogram of lean body mass during interdialysis time periods. A highly significant correlation was observed in patients not receiving antihypertensive medication (untreated group).

Normal distribution in the population, with a mean value of $0.225 ± 0.19\%$ per ml.kg$^{-1}$ of volume expansion (Figure 2). It was similar in men ($0.23 ± 0.19$) and women ($0.21 ± 0.20$) ($P = \text{NS}$). Eleven of 120 patients presented negative values of sensitivity.

Sensitivity of diastolic BP was modified by two factors. It was less marked in patients with a relatively high initial level of DBP ($r = −0.36, P < 0.0001$). Moreover, DBP sensitivity correlated negatively with the serum potassium concentration ($r = −0.35, P < 0.02$). The latter association was only significant in women (Figure 3). On the other hand, systolic BP sensitivity was unrelated to the initial SBP and the serum potassium values. Sensitivity did not correlate with age,
those with two kidneys: $0.19 \pm 0.2$ and $0.23 \pm 0.2\%$ per ml.kg$^{-1}$ respectively ($P=NS$).

**Final BP level**

Seventeen patients (14%) were classified as hypertensive (final MBP $>107$ mmHg) and 103 patients (86%) were considered to be normotensive. The MBP attained at the end of the period was unrelated to interdialysis expansion of volume. Hypertensive and normotensive patients gained similar interdialysis volumes: $36 \pm 20$ and $35 \pm 13$ ml.kg$^{-1}$ respectively ($P=NS$). On the other hand the regression line indicating the relationship between the interdialysis increment in MBP and volume expansion had a steeper slope in hypertensive subjects, $b=0.34 \pm 0.07$ (SE), than in normotensive patients, $b=0.16 \pm 0.04$, indicative of a greater volume sensitivity in the former than in the latter (Figure 4).

The mean sensitivity in the hypertensive group was $0.35 \pm 0.2$, compared with $0.20 \pm 0.19\%$ per ml.kg$^{-1}$ in the normotensive group ($P<0.005$). No negative values of sensitivity were found among hypertensive subjects.

Patients with hypertensive values of final MBP began the period with greater BP values than normotensive patients: $101 \pm 7$ vs $87 \pm 11$ mmHg ($P<0.00001$).

Final MBP was significantly greater in patients with vascular or glomerular renal disease (including diabetes) than in those with tubulointerstitial (including polycystic) renal disease: $98 \pm 11$ vs $93 \pm 13$ mmHg ($P<0.03$). A direct correlation was found between the final DBP and the haematocrit values ($r=0.22$ $P<0.01$). The small number of patients on rHuEpo treatment was insufficient to analyse differences in BP between Epo-receivers and non-receivers.

Stepwise multiple linear regression was used to examine the simultaneous effect of seven independent continuous variables on final MBP. Included variables were age, initial MBP, basal overhydration, serum urea, potassium and calcium and haematocrit. Stepwise selection found that initial MBP was a strong determinant of final MBP level; to a smaller extent, the predialysis serum urea appeared as an additional independent factor (with a positive coefficient) of final pressure (Table 3).

**Discussion**

The present study aimed to identify the change in BP corresponding to the volume load during interdialysis.

### Table 3. Predictive factors of mean blood pressure at the end of interdialysis time period (final MBP)

<table>
<thead>
<tr>
<th>Coef.</th>
<th>SE</th>
<th>$t$ value</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial MBP</td>
<td>0.916</td>
<td>0.045</td>
<td>20.4</td>
</tr>
<tr>
<td>Serum urea</td>
<td>3.83</td>
<td>1.89</td>
<td>2.03</td>
</tr>
</tbody>
</table>

ANOVA $R^2=0.79$; $P=0.000$. 

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Fig. 2. Distribution of percentage MBP responses to the volume gain (sensitivity) in 120 haemodialysis patients. Blood pressure increase was observed in 91% of the patients.

Fig. 3. Negative correlation of DBP sensitivity with the initial DBP level and with serum potassium concentration.
Fig. 4. Relationships between percentage MBP changes and volume expansion during interdialysis time periods in hypertensive and normotensive patients. A steeper slope of the regression line, indicative of a greater volume sensitivity of BP, is observed in the hypertensive group compared to the normotensive group (P<0.005).

time periods. If the individual variability of BP is similar or greater than BP differences between individuals, the measurement error can attenuate or even mask correlations between this parameter and other variables in the group under study (regression-dilution bias) [14]. Attenuation of association is reduced by increasing the number of measurements [15]. Furthermore, by taking the average of 25 consecutive BP and volume measurements a more reliable and reproducible individual BP response should be obtained.

In the population under study, the expansion of total body fluid volume showed a significant association with MBP gain, accounting for 20% (r = 0.45) of the total change of BP. A similar correlation (r = 0.49) between the increase in extracellular volume and the increase in MBP in 23 patients with moderate or severe renal failure [6] was found by Koomans et al. In contrast, subsequent studies monitoring interdialysis ambulatory BP are at variance with our finding. Luik et al. found that the rise of BP from the first to the last day of the interdialysis period (2 to 3 days), did not correlate with the absolute weight gain [8]. Similarly, Chazot et al. [9], who examined BP differences between the mean levels of the first and the second diurnal periods in night-time treated haemodialysis patients, found no correlation between the rise in BP and the interdialysis weight gain; the same was find for nocturnal periods in day-time treated patients. Differences in methodology, including patient numbers, could account for these apparent discrepancies. Changes between mean levels of BP on first and last days may be less marked than the difference between BP readings at the extreme points of interdialysis time periods. The exclusion of patients on antihypertensive treatment probably avoids an important confounder for the study results.

The volume sensitivity of each patient was calculated as the BP response per unit of volume expansion. This is different from sodium sensitivity of BP as it has been described for normal renal function. Sodium sensitivity of BP is usually referred to as a fixed change of sodium intake [16], but not as a change of volume, which varies depending on each individual’s ability to excrete sodium and water [17]. The evidence supports that essentially all of the increase in BP occurring after sodium retention can be explained by increases in extracellular fluid volume [18] and that sodium per se has a very small, if any, direct effect on blood vessels total body fluid volume showed a significant association with MBP gain, accounting for 20% (r = 0.45) of in elevating BP [19]. Thus by examining the sensitivity of BP to volume gain, we assess a parameter directly affecting BP. This may be important in haemodialysis patients whose volume retention is by no means proportional to sodium retention.

The existence of large interindividual differences in sensitivity clearly argues for the existence of factors other than volume contributing to the BP response. The distribution of body fluids (influenced by interstitial and venous compliance), the changes in venous filling pressure, the related changes in cardiac output, and the neurohumoral adjustments of peripheral resistance are main determinants of the final BP. Their importance in the regulation of BP in uraemia has not been analysed in this study. Koomans et al. found that sensitivity to extracellular fluid volume expansion was greater in severe than in moderate renal failure, and this high sensitivity was associated with an increased plasma volume/interstitial fluid volume ratio [6]. When examining the role of plasma renin activity (PRA) in haemodialysis patients, Igarashi et al. observed that patients with high PRA (prior to a volume load) easily increased BP during volume expansion, whereas patients with a low to normal PRA did not [20]. The
dependence of BP on blood volume could also be determined, in part, by the balance between the flow-dependent vasodilatation mediated by nitric oxide (NO) and the myogenic vasoconstriction [21]. Defective synthesis of the vasodilator NO has been observed in chronic renal failure [22] and this could be involved in enhanced volume sensitivity.

We observed that the sensitivity of DBP was less marked in patients who began the period with elevated levels of DBP. Assuming that DBP is an approximate index of peripheral vascular resistance, increments in DBP during volume expansion (diastolic sensitivity) would represent the rise in resistance induced by volume. This process, called whole-body circulatory autoregulation [23], probably occurs early during the interdialysis period: peripheral resistance increased in the first two days of volume expansion in anephric men [24], and after 24 h in dogs with reduced renal mass subjected to a sustained excess volume load [25]. Our results demonstrate a limiting effect of the elevated arteriolar tone on the autoregulatory process.

Serum potassium also decreased DBP sensitivity, possibly by reducing vasoconstriction. It has been demonstrated that hyperkalemia produces vasodilatation by a direct effect on arterial smooth muscle [26]. We observed a significant association only in women. Serum calcium concentration was not found to exhibit an overt influence on volume sensitivity in this study, and the generally recognized effect of age on sensitivity might have been obscured by the high mean age of our population.

Recently it has been pointed out that a 70% reduction of renal mass does not modify the autoregulatory response to acute volume expansion [27]. In our group of patients with subtotal nephrectomy and practically no residual renal function, volume sensitivity was similar to sensitivity observed in the rest of the population.

Studies exploring the sensitivity of BP regularly find a small percentage of individuals who do not increase their BP after a volume load, including chronic renal failure patients [6]. Nearly 9% of the patients of the present study had negative values of sensitivity. It has been proposed that heart failure or hypoalbuminaemia are conditions under which elevated extracellular fluid volume would not increase BP in uraemia [28].

The final level of BP probably overestimates the representative BP value in haemodialysis patients [7]. In our study the final BP, which was the highest observed BP level in 91% of the patients, was independent of volume expansion and basal overhydration. Volume gain correlated with the change in BP but not with the absolute level of BP. Coincidently, Chazot et al. [9] observed that circadian BP (averaged mean over 24 h) did not correlate with interdialysis weight gain or weight gain/dry weight ratio. Sherman et al. [10] found an only minimal effect of excess interdialysis weight on predialysis BP level.

The relationship observed between final DBP levels and haematocrit suggests an increment in peripheral resistance with increasing haematocrit values, an effect that is explained by the loss of hypoxic vasodilatation. The main determinant of final MBP was the initial MBP level. The weak positive association found in the present study between final BP and plasma urea concentration could argue in favour of a parallel accumulation of pressor substances in uraemia [29].

In summary, our results give a measure of the influence of interdialysis weight gain on BP and support the importance of an adequate control of volume balance, particularly in highly volume-sensitive patients. Further study is necessary to identify other factors controlling the BP response in uraemia.

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