Factors associated with poorly-controlled hypertension in continuous ambulatory peritoneal dialysis patients

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ABSTRACT

Introduction: Hypertension is highly prevalent among continuous ambulatory peritoneal dialysis (CAPD) patients and is a major risk factor for cardiovascular complications. This study examines the risk factors associated with poorly- controlled hypertension in CAPD.

Methods: We performed a cross-sectional study of 66 stable adult CAPD patients to evaluate their hypertension control over a period of three to four months and their associations with other clinical and laboratory parameters.

Results: The mean age of the patients was 56.7 (±1.27) years. Their mean systolic and diastolic blood pressure were 139 (±2.59) mmHg and 77 (±1.35) mmHg respectively; 71 percent of them were on antihypertensive drugs. Thirty (45.5 percent) patients had high blood pressure greater than 140/90mmHg. Compared with patients with normal blood pressure, patients with high blood pressure received significantly more antihypertensive drugs (p-value equals 0.034) and were more likely to be clinically overloaded (p-value less than 0.001). Multivariate analysis showed that systolic blood pressure was predicted by volume expansion (p-value less than 0.001) while diastolic blood pressure was negatively predicted by age (p-value equals to 0.004). In addition, volume overload was predicted positively by dialysate/plasma creatinine (p-value equals 0.011) and negatively by serum albumin (p-value less than 0.001).

Conclusion: Clinically-apparent volume overload was associated with poor systolic blood pressure control despite aggressive antihypertensive drug therapy. This finding underlines the importance of fluid control and could provide an explanation of the poor outcome observed in patients with high peritoneal transport.

Keywords: continuous ambulatory peritoneal dialysis, hypertension, peritoneum, ultrafiltration

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INTRODUCTION

Atherosclerotic and cardiovascular disorders are the major causes of morbidity and mortality in dialysis patients. While their development is multifactorial, hypertension could be one of the most important factors[1]. Volume overload has been shown to be an important contributing factor for the persistence of hypertension among dialysis patients. Studies have shown that strict volume control could normalise blood pressure in a large number of dialysis patients[2,3]. Nevertheless, attainment of euvolemic state is not always easy and successful. A successful outcome depends on accurate determination of dry weight, efficacious dialysis, preservation of residual renal function and good patient compliance.

On the other hand, there is little data on the status of blood pressure control and response to antihypertensive drug therapy in continuous ambulatory peritoneal dialysis (CAPD) patients with clinical volume expansion. It is also unclear whether other factors, apart from volume overload, that might significantly affect blood pressure control. Therefore, we performed a cross-sectional study on our CAPD patients to delineate the exact impact of clinically-detectable volume expansion on blood pressure control, and to identify significant factors that could contribute to volume overload and poor blood pressure control with drugs.

METHODS

The study was conducted at a regional dialysis center in January 1999. All patients older than 18 years old who received CAPD treatment for more than six months were eligible for the study. The exclusion criteria were occurrence of peritonitis in the last four months, severe myocardial dysfunction with ejection fraction less than 35% measured by two-dimensional echocardiography, a history of right heart failure, and presence of severe malnutrition evidenced by a serum albumin level <20g/L.

A total of 90 Chinese CAPD patients was screened and 66 were recruited into the study. 24 patients were excluded because of recent peritonitis, significant myocardial dysfunction and severe malnutrition. The

Table I. Causes of renal failure in 66 continuous ambulatory peritoneal dialysis patients.

Diagnosis	No.(%)
Diabetic nephropathy	15 (22.7%)
Chronic glomerulonephritis	10 (15.2%)
Hypertensive nephropathy	7 (10.6%)
Immunoglobulin A nephropathy	2 (3%)
Ischaemic nephropathy	1 (1.5%)
Nephrolithiasis	2 (3%)
Polycystic kidney disease	3 (4.5%)
Lupus nephritis	1 (1.5%)
Unknown	25 (38%)

Table II. Dialytic and clinical parameters of continuous ambulatory peritoneal dialysis patients.

Parameter	Mean ± SD
Haemoglobin (g/dL)	8.8 ± 0.2
Parathyroid hormone (pmol/L)	23.2 ± 3
Serum albumin (g/L)	32.2 ± 0.4
Total weekly Kt/V	1.93 ± 0.06
Renal weekly Kt/V	0.38 ± 0.06
nPNA (g/kg/d)	1.34 ± 0.05
D/P creatinine	0.74 ± 0.02
Peritoneal transport classification by D/P creatinine ratio	No. (%)
High (0.82 - 1.03)	18 (27.3%)
High average (0.66 - 0.81)	32 (48.5%)
Mean (0.65)	2 (3%)
Low average (0.5 - 0.64)	14 (21.2%)
Low (0.34 - 0.49)	0 (0%)

D/P creatinine ratio: dialysate to plasma creatinine ratio; nPNA:normalized protein equivalent of nitrogen appearance; SD: standard deviation; weekly Kt/V: weekly fractional urea clearance.

demographical data recorded included race, gender, age, diabetic status and underlying renal disease. The parameters studied included the mean clinic blood pressure, haemoglobin level, serum albumin level using the bromcresol green method, intact parathyroid hormone level, peritoneal transport characteristics, dialysis adequacy indices, clinical evidence of volume overload, treatment with recombinant human erythropoietin, number of antihypertensive agents and CAPD regimes.

The underlying causes of renal failure are shown in Table I. All patients received dietary advice on salt intake not exceeding 3g to 4g a day. Sixty patients received Dianeal (Baxter Healthcare, McGraw Park, IL, USA) dialysate solution with sodium content of 132 mEq/L. Six patients received Fresenius standard dialysis solutions CAPD 2, 3 and 4 (Fresenius Medical Care, Bad Homburg, Germany) with sodium content of 134 mEq/L. Eleven patients had 3 daily and 55 had 4 daily 2-litre CAPD exchanges. The prescriptions for 1.5%, 2.5% or 4.25% Dianeal solution and 1.5%, 2.3% or 4.25% Fresenius dialysis solution were determined by the attending physicians trying to achieve fluid balance.

The mean systolic and diastolic blood pressure levels were abstracted as the mean of the last three values from the patient's outpatient record as at the first week of January 1999. The clinic blood pressure was routinely measured in the sitting position after a rest of at least 15 minutes during each outpatient visit using a non-invasive semi-automatic blood pressure monitor (Dinamap, Critikon Inc., Miami, FL, USA).Volume overload was assumed if pedal oedema and/or elevated jugular venous pressure were present on two or more follow-ups as at the first week of January 1999. All observations were made by the attending physicians who were not involved in the measurement of blood pressure.

Peritoneal membrane transport was expressed by the 4-hour dialysate/plasma creatinine ratio (PET) according to the fast peritoneal equilibration test of Twardowski[4]. The dialysate/plasma creatinine results were then used to classify patients as low, low average, mean, high average and high membrane transporters accordingly[5]. The locally validated glucose correction factor for dialysate creatinine assay was used.

Adequacy of dialysis was estimated by calculating the total weekly fractional urea clearance (Kt/V), which is a dimensionless ratio derived from total weekly urea clearance normalized to total body water content. The total water content was estimated from the patient's sex, height, weight and age[6]. Peritoneal and renal urea clearances were estimated from 24-hour urine dialysate urea and serum urea concentration at the end of collection. According to Bergstrom's formula, the protein equivalent of nitrogen appearance (PNA) was normalised (nPNA) according to the idealised body weight[7].

The results are expressed as mean ± standard deviation. Differences between groups were assessed using Fisher's exact test, Chi-square test and Mann-Whitney U test when appropriate. Linear multiple regression, and multiple logistic regression models, coupled with backward stepwise selection method, were used for multivariate analysis; with possible predictors identified by correlations using Spearman's correlation coefficient. A value of $p<0.05$ is considered statistically significant.

Table III. Dialytic and clinical parameters between high blood pressure (BP>140/90) and normal blood pressure (BP≤140/90) groups.

Variable	HBP (n=30)	NBP (n=36)	p-value
Age (years)	57.4 ± 2	56.1 ± 1.6	NS
Body weight (kg)	56.6 ± 2.7	56 ± 1.6	NS
Sex (Male/female)	17/13	17/9	NS
Diabetes mellitus	9 (30%)	10 (27.7%)	NS
rHuEPO	4 (13%)	8 (22%)	NS
Fresenius dialysis solution	2 (6.7%)	4 (11.1%)	NS
Daily exchanges	3.2 ± 0.7	3.14 ± 0.6	NS
Duration on dialysis (months)	35.3 ± 2.8	37.3 ± 4.3	NS
Number of anti-hypertensives	2 ± 0.3	1.3 ± 0.2	0.034
Volume overload	19 (63%)	4 (11%)	<0.001
Residual urine output (L/d)	0.47 ± 0.1	0.5 ± 0.1	NS
D/P creatinine	0.76 ± 0.02	0.73 ± 0.02	NS
Weekly Kt/V			NS
Total	1.8 ± 0.1	1.9 ± 0.1	NS
Renal	0.37 ± 0.07	0.39 ± 0.09	NS
nPNA (g/kg/d)	1.4 ± 0.09	1.29 ± 0.06	NS
Haemoglobin (g/dL)	8.5 ± 0.3	9.1 ± 0.3	NS
Serum albumin (g/L)	31.3 ± 0.5	33 ± 0.5	0.031
iPTH (pmol/L)	19.6 ± 3.5	26.2 ± 4.6	NS

rHuEPO: recombinant human erythropoietin; D/P: dialysate to plasma ratio; weekly Kt/V: weekly fractional urea clearance; nPNA: normalised protein equivalent of nitrogen appearance; iPTH: intact parathyroid hormone; HBP: high blood pressure; NBP: normal blood pressure.

RESULTS

Of the 66 patients, 19 (28.8%) were diabetics and 12 (18.2%) patients were receiving recombinant human erythropoietin therapy. Their mean duration on CAPD treatment was 39 ± 2.68 months. Thirty-nine (59%) patients had residual urine output >100mL daily and were receiving daily oral diuretic therapy. Of these, 23 (34.8%) were clinically volume overload. Thirty (45.5%) patients had blood pressure levels >140/90mmHg. The mean systolic and diastolic blood pressure levels of all patients were 139 ± 2.59mmHg and 77 ± 1.35mmHg, respectively. Forty-six (69.7%) patients received at least one antihypertensive drug. The results of the other parameters are shown in Table II.

There were no differences in the demographical characteristics between patients with high blood pressure and those with normal blood pressure (Table III). More patients with high blood pressure had clinically detectable volume overload (p<0.001). At the same time, the serum albumin level of patients with high blood pressure was significantly lower than those with normal blood pressure (p=0.031). There was no difference in the intensity of dialysis received in terms of the total volume of daily exchanges, dialysis adequacy indices (total and renal weekly urea clearance), nitrogen appearance and dialysate/plasma creatinine (p>0.05). Both groups also had similar residual urine output, haemoglobin level, intact parathyroid hormone level and the same number of patients receiving erythropoietin therapy (p>0.05). Nevertheless, the patients with high blood pressure had been receiving significantly more antihypertensive drugs than those with normal blood pressure (p=0.034).

Linear multiple regression analysis showed that both systolic and diastolic blood pressure were closely correlated (r=0.52, p<0.001). Apart from that, volume overload (r=0.58, p<0.001) was a predictor of systolic blood pressure. Age (r=-0.254, p=0.04) was a negative predictor of diastolic blood pressure. Multiple logistic regression analysis revealed that clinical volume overload was predicted by dialysate/plasma creatinine ratio(r=0.31, p=0.011) and low serum albumin level (r=-0.45, P<0.001), in addition to systolic blood pressure (r=0.58, p<0.001) and the number of anti-hypertensive drugs (r=0.52, p<0.001).

Among the 18 patients with dialysate/plasma creatinine ratio between 0.82 and 1.03 (high peritoneal membrane transport), 11 of them had volume overload.

Compared with those seven patients without volume overload, the 11 patients with volume overload had a significantly higher systolic pressure (157.7 ± 18mmHg versus 126.2 ± 16.5mmHg, p=0.003).

DISCUSSION

Volume expansion has been regarded as one of the most important causes for dialysis-refractory hypertension[8], with studies showing that normotension could be achieved by adequate volume control[2,9]. Therefore, attainment of dry weight has become an integral goal for haemodialysis. Similarly, a target or desired weight for CAPD patients has become an important goal for dialysis adequacy[10]. However, the determination of dry or desired weight for an individual patient is not straightforward. The definition remains uncertain and multiple clinical definitions have been proposed[11,12].

In order to have an accurate determination of dry weight, some new non-clinical methods such as bioimpedance plethysmograph, measurement of inferior vena cava diameter, plasma atrial natriuretic peptide concentrations and blood volume have been proposed. Nevertheless, each of these methods has its own inherent bias and may not be readily available in day-to-day clinical practice. After all, the determination of dry weight remains a clinical judgement and the absence of oedema does not rule out the presence of hypervolaemia[13].

Given the limitations of the concept of a desired weight, this study examined the problem from a clinical perspective and one of the aims was to study the implications of patients with and without clinical evidence of volume overload in their blood pressure control. Nevertheless, observational bias and errors could also arise in our clinical criteria. We sought to minimise these by excluding patients who had myocardial failure or severe hypoalbuminaemia.

The findings in this study illustrated the impact of clinically- detectable volume expansion on blood pressure control. Two mechanisms are thought to account for volume- related hypertension in overhydrated patients, namely: an increase in cardiac output and an elevated systemic vascular resistance. While it is unknown which mechanism is more dominant, it seems that in severe volume expansion, hypertension is refractory to control, even with aggressive treatment using multiple antihypertensive agents.

In a dialysis patient with preserved renal function, residual urine output sometimes could contribute to significant daily fluid removal. We did find any difference in the residual urine output and renal urea clearance between the overloaded and non-overloaded patients in our study. This finding may be due partly to the relatively long duration (mean 39 months) of our study population which resulted in a relatively small volume of residual urine ($\leq$100mL/day in 41% of patients) among our patients. In these patients, peritoneal ultrafiltration accounted for much fluid removal and impaired peritoneal ultrafiltration might have predisposed them to fluid retention.

Apart from causing poor ultrafiltration capacity, a high peritoneal transport rate is also known to be associated with increased protein losses resulting in hypoalbuminaemia, increased glucose absorption with hyperinsulinism, local advanced glycosylate end-product formation and the development of an atherogenic lipid profile[14,15]. Increased peritoneal membrane transport is also shown to be associated with decreased technique and patient survival[16,17]. While the underlying mechanism remained speculative, increased peritoneal protein loss and volume expansion are thought to be possible contributory factors. With a strong association noted between volume overload and poor controlled systolic blood pressure within the subgroup of patients with a high peritoneal transport, the findings in this study also support this speculation.

Apart from fluid retention, other important factors may explain blood pressure control. A recent study has shown that patients on long, slow haemodialysis, normotension could also achieve normotension in overload status. Vasoactive factors removed by the long and slow process of dialysis were implicated[3]. Luik AJ et al also suggested that the duration of dialysis might have an independent beneficial effect on blood pressure control[18]. While all these studies were done on haemodialysis patients, it is not known whether this is true in patients on CAPD. In our study, we did not find a significant relationship between the blood pressure control and total weekly urea clearance. Volume overload remained the major predictor of poorly-controlled systolic blood pressure.

Diastolic blood pressure is regarded to be more important than systolic blood pressure. Recent studies, however, have shown that the latter is a bigger risk factor for cardiovascular events than high diastolic blood pressure. In our study, diastolic blood pressure was significantly associated with systolic blood pressure, and it did not seem to be independently predicted by any other factor except age. Our observations are consistent with the data from the Framingham Heart Study, which demonstrated that both diastolic and systolic blood pressure increased with age. However, diastolic blood pressure peaked between 50 to 60 years of age, and decreased thereafter. It was thought to be associated with the development of large artery stiffness in middle age and in the elderly[19]. The negative relationship between the diastolic blood pressure and

age in our study may be related to the relatively old age (mean age 56 years old) of the subjects, or it may reflect accelerated vascular ageing among our patients.

Volume expansion is greatly responsible for refractory hypertension in our CAPD patients; blood pressure was difficult to control, even with multiple antihypertensives. On the other hand, although an oedema-free state might not equate to euvolaemia and render a patient normotensive, it did help to control hypertension with medications. Other factors may contribute to persistent hypertension in CAPD patients. Nevertheless, their effects are likely to be less dramatic and are more amenable to antihypertensive drug therapy, rendering them undetectable in this study. This study also confirms the affinity between volume expansion and high peritoneal transport. In patients with high peritoneal transport, optimisation of fluid control should be attempted aggressively so that it might partially reverse the associated poor outcome.

Nevertheless, there are several limitations in this study. Firstly, the method for detecting volume overload by clinical examination in this study was subjective and susceptible to observation bias. Besides, although we had excluded those patients with severe hypoalbuminaemia, there could be some patients having pedal oedema secondary to mild hypoalbuminaemia being classified as volume overload. Furthermore, there are some other factors such as the renin-angiotensin system and autonomic dysfunction which might affect the blood pressure control. These may have confounded the findings but have not been examined in this study. Therefore, further study is required before definite conclusions could be drawn on this issue.

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