Cardiovascular disease is a leading cause of death in patients with end-stage renal disease. Uncontrolled hypertension and volume expansion contribute to alterations in left ventricular geometry and are independent predictors of poor survival in dialysis patients. Excessive salt intake is a major handicap with loss of residual renal function. Sodium removal becomes inadequate in the face of declining residual renal function. Continued salt intake and inadequate sodium removal lead to volume expansion, which aggravates arterial hypertension. In part I of this two-part review, we consider information on dietary salt intake and its relationship to blood pressure and volume control in peritoneal dialysis (PD) patients. In addition, we review recently published studies on the use of various PD modalities to remove sodium, emphasizing the significance of volume expansion and uncontrolled hypertension in PD patients. Part II reviews the various measures available to enhance sodium and fluid removal in PD patients.

Key words
Hypertension, sodium removal, residual renal function, diuretics, low-sodium dialysis solutions

Introduction
Cardiovascular disease is a leading cause of death in end-stage renal disease (ESRD) patients (1). According to recent studies, patients on peritoneal dialysis (PD) are prone to develop hypertension and volume overload, especially after the first 2–3 years of dialysis, which often coincides with the loss of residual renal function (RRF) (2,3). Excessive intake of dietary salt stimulates thirst and contributes to volume expansion and hypertension. Such intake becomes a major handicap once patients lose RRF, and PD becomes the only means to remove excess sodium. Under those circumstances, sodium removal by standard CAPD probably becomes inadequate. Removal is even more limited in patients on automated peritoneal dialysis (APD) (4).

This article reviews the available information regarding salt intake and its relationship to hypertension, prevalence of hypertension, and volume expansion in PD patients. It also examines the impact of excessive salt intake on cardiovascular morbidity and mortality.

Dietary salt intake and its relationship to hypertension
Reduced salt intake is associated with a fall in blood pressure in people with or without hypertension, in black people and in people of other races, and in both women and men (5). Increased dietary salt intake contributes to hypertension and also exerts some effects on left ventricular mass unrelated to arterial blood pressure (6).

No consensus exists on recommended salt intake in PD patients. Initially, peritoneal dialysis was considered to be a continuous process, offering excellent blood pressure (BP) and volume control. Therefore, a common practice was to allow liberal salt and water intake in PD patients. However, a number of recent studies have shown that subclinical volume expansion is common in PD patients. That subclinical expansion is, in turn, responsible for hypertension (7,8). The effects become more obvious once RRF is lost. Excessive dietary salt intake contributes to uncontrolled hypertension and volume overload.

Gunal et al. (9) studied 47 hypertensive patients on PD who were maintained on strict dietary salt re-
striction after stopping antihypertensive treatment. In most of the patients, weight decreased and BP fell significantly. On the other hand, Fine et al. (10) argued that, in PD patients, salt intake is much too restricted. In a prospective, double-blind crossover study, the Fine group looked at the effect on weight and BP of additional salt (60 mmol daily) in divided doses in 20 continuous ambulatory peritoneal dialysis (CAPD) patients. Systolic and diastolic BP increased to $153 \pm 14$ mmHg and $84 \pm 11$ mmHg from $140 \pm 21$ mmHg and $79 \pm 7$ mmHg respectively. Weight increased to $76 \pm 11$ kg from $75 \pm 9$ kg.

**Volume expansion and hypertension**

**Concept of target weight**

Target weight and dry weight are not uniformly defined for dialysis patients.

Blumberg et al. (11) defined dry weight as the body weight at which extracellular fluid volume is at or near normal, but not less than normal. According to Charra et al. (12), dry weight means the end-of-dialysis weight at which the patient can remain normotensive until the next dialysis despite interim retention of salt and water. The International Society for Peritoneal Dialysis (ISPD) ad hoc committee on ultrafiltration (13) defines target weight in a PD patient as “the weight at which the patient is euvoletic.” The committee recommends that the term “dry weight” should be replaced by “target weight” or “desirable weight,” there being no need to keep the patient dry because of the continuous nature of peritoneal dialysis. However, the committee further recommends pursuit of weight reduction beyond the edema-free state, because the edema-free state does not correlate with euvoletic. Such a reduction is especially important in a hypertensive patient to correct the volume-related component.

Dry weight is difficult to assess in PD patients. Clinical examination is often unreliable. In other words, an absence of symptomatic fluid retention or edema does not rule out subclinical volume expansion (14). In PD patients, it is often difficult to decide on clinical grounds alone whether weight gain is due to accumulation of fluid or an increase in adipose tissue. Indeed, the volume status of PD patients can be viewed as a spectrum ranging from dehydration on one end to severe overhydration on the other (Table I).

<table>
<thead>
<tr>
<th>Volume status</th>
<th>BP</th>
<th>Antihypertensive drugs</th>
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<tbody>
<tr>
<td>Severe volume depletion</td>
<td>Low</td>
<td>No</td>
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<tr>
<td>Mild-to-moderate volume depletion</td>
<td>Low or normal</td>
<td>No</td>
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<tr>
<td>Euvolemia</td>
<td>Normal</td>
<td>No</td>
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<td>Euvolemia</td>
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<tr>
<td>Euvolemia</td>
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<tr>
<td>Mild-to-moderate volume expansion</td>
<td>High</td>
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<td>Severe volume expansion</td>
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Most of our patients look clinically euvoletic, but show normal BP or hypertension requiring drug therapy. Subclinical volume overload is now recognized as common in PD patients who look deceptively normal on clinical examination (7,8). Importantly, a significant number of patients exhibit signs of overhydration, a scenario that often develops after loss of RRF. In contrast, the few patients who are normotensive without drugs are often in a “honeymoon period” with substantial RRF. Weight gain from the extra calories provided by the glucose absorbed from the dialysis solution further compounds the situation. That gain tends to occur in the first year after initiation of PD and stabilizes thereafter.

Various methods are used to estimate the fluid status of dialysis patients. Those methods include cardiothoracic ratio (CTR), inferior vena cava (IVC) diameter, left atrial (LA) size, atrial natriuretic peptide (ANP) level, bioelectrical impedance analysis (BIA), and measurement of plasma volume by $^{131}$I. (Full descriptions of the methods are beyond the scope of this review.)

**Volume expansion in PD patients**

Emerging evidence suggests that volume expansion is the essential factor in the genesis and maintenance of hypertension in PD patients. The volume expansion becomes obvious once RRF is diminished or lost. In some patients, the expansion is attributable to increased peritoneal membrane capillary permeability. High transporters, characterized by a poor ultrafiltration rate, have been shown to have poor survival rates despite having good urea and creatinine clearances (15–19). That poor survival is attributable mainly to ultrafiltration failure and consequent fluid overload, which leads to hypertension, left ventricular hyper-
Volume Expansion and Sodium Balance in PD (Part I)

trophy (LVH), and increased cardiovascular mortality. No studies to date have looked at the impact of high transport status on overall sodium removal. We herewith review some of the studies that demonstrate the presence of excess fluid in PD patients.

Lameire et al. (20) observed body weight in 28 PD patients before and after transfer to hemodialysis (HD) for up to 3 months and found that weight decreased to 62.4 ± 2.4 kg from 66.6 ± 2.3 kg and that diastolic BP fell to 76 ± 1.3 mmHg from 82 ± 2.3 mmHg. The authors did not discuss the reasons for transfer from PD to HD.

Issad et al. (21) analyzed data on CAPD patients undergoing renal transplantation. The Issad group measured hemodynamic parameters [such as mean pulmonary artery pressure (PAP)] to tailor intravenous fluids administered before transplantation. Strikingly, mean PAP was ⊕25 mmHg and ⊕30 mmHg in 36% and 14.6% of CAPD patients respectively (average: 21.1 ± 7.4 mmHg). Even more important, the initial mean PAP appeared to be higher (21 ± 7.4 mmHg) in patients on CAPD than in those on HD (16.3 ± 7.6 mmHg).

Faller et al. (18) demonstrated the link between volume expansion and reappearance of hypertension. That group studied the relationship between plasma volume and BP in 25 stable CAPD patients during their first year on PD, and they followed the same cohort in their fourth and fifth years. Plasma volume was first measured before the start of CAPD. During the first year, plasma volume decreased by more than 10% in most patients and BP fell. In contrast, during the fourth and fifth years, plasma volume increased by more than 10% and BP rose (22).

The Web Study Group from Japan examined 203 PD patients from 21 centers to detect the presence of face and leg swelling, heart failure, and pleural effusion. They measured atrial natriuretic peptide (ANP) and CTR to assess hydration status. The subjects were divided into “adequate,” “mild,” “moderate-to-severe” overhydration. Among the study patients, 67% were adequately hydrated, 23.6% showed mild overhydration, and 9.4% showed moderate-to-severe overhydration (23).

Enia et al. (8) measured ANP levels and various echocardiographic parameters to assess plasma volume in 51 CAPD and 201 HD patients. Plasma ANP level and left atrial volume were significantly higher in CAPD patients. Similarly, the number of patients requiring treatment for hypertension was higher in the CAPD group. Left ventricular hypertrophy was present in 86% of CAPD patients as compared with 62% of HD patients.

These studies clearly show that a significant number of patients on PD exhibit clinical signs of volume overload. An even a larger proportion may be suffering from subclinical volume expansion that goes undetected. Physicians should look carefully for subtle signs of volume expansion when a previously normotensive PD patient develops new-onset hypertension or worsening BP control.

Peritoneal dialysis and hypertension
Earlier studies in PD patients reported excellent short-term BP control (24). Now, growing evidence suggests that BP control either worsens or that patients require more antihypertensive medications after the first few years on PD.

Faller and Lameire (22) studied a cohort of 23 patients on CAPD over a 7-year period. They found no difference in BP over that time, but they noted an increase in the use of antihypertensive drugs.

Recently, in a cohort of PD patients, Menon et al. (3) from our unit evaluated long-term BP control and the factors associated with poor control. Of 207 patients, 91.3% were hypertensive at the start of treatment. Systolic and mean arterial pressure declined and reached a nadir between 6 months and 1 year. Those readings then steadily and progressively worsened throughout the remaining follow-up (Figure 1). Multiple linear regression analysis showed that duration of hypertension, declining RRF, and residual urine output were independently associated with poor BP control.

Cocchi et al. (25) studied the prevalence of hypertension in a large Italian multicentric study and found that hypertension was prevalent in 88.1% of the PD population. One third of patients had moderate-to-severe hypertension.

The foregoing studies clearly show that hypertension is highly prevalent in the PD population and is poorly controlled despite antihypertensive treatment.

Sodium removal in peritoneal dialysis
CAPD VERSUS APD
The presence of RRF adds substantially to sodium removal. Once RRF is lost, sodium removal during
PD depends mainly on convection and diffusion. The standard concentration of sodium in PD solution is 132 mmol/L (as compared with a plasma sodium concentration of 140 mmol/L). Owing to the small concentration gradient, less sodium is removed by diffusion than by convection. Sodium removal varies among the various modalities of peritoneal dialysis, mainly because of the differences in osmolality of the fluids used (1.5% vs. 4.25%) and in the dwell time.

Leypoldt (26) and Struijk and Krediet (27) described the physiology of sodium transport and the phenomenon of “sodium sieving” during PD. Sodium sieving occurs because transcellular water without sodium is transported through the ultrasmall pores (now known as aquaporin I) or because sodium is bound to interstitial tissues. As a result, in the earlier part of the exchange, the sodium concentration in the dialysate falls mainly due to dilution from the ultrafiltrate (which has a low sodium concentration owing to sieving). That dilution increases the concentration gradient and leads to enhanced diffusion of sodium during the rest of the dwell period.

In APD, with its rapid exchanges performed over 8 – 10 hours, the dwell time is short. Little time is therefore available for diffusion. In addition, use of hypertonic exchanges during APD leads to a more pronounced fall in dialysate sodium concentration. That fall might lead to greater sodium removal because of enhanced diffusion, but only if the dwell time is long enough. In contrast, if the dwell time is too long, sodium loss is again reduced because of fluid and sodium reabsorption. For those reasons, sodium removal in APD is lower than in CAPD, and sodium loss in APD does not correlate well with fluid removal. In other words, it may be possible to achieve good ultrafiltration with the use of hypertonic exchanges in APD and still have inadequate sodium removal.

Several recent studies have demonstrated that phenomenon. Ortega et al. (28) performed 53 sodium-balance studies (23 in CAPD and 30 in APD) in 36 stable PD patients. Peritoneal sodium removal was higher in CAPD than in APD (195 ± 80 mEq vs. 87 ± 86 mEq, p < 0.0001). The net ultrafiltration was higher in CAPD than in APD and was strongly correlated with peritoneal sodium removal. Plasma sodium and urine sodium were similar in the two groups. Interestingly, more patients were on antihypertensive treatment in the APD group than in the CAPD group. The systolic blood pressure was higher in the APD group than in the CAPD group, but the difference did not reach statistical significance (28). In another study, Rodriguez-Carmona et al. (4) examined sodium removal in a sequential design in three phases: study A was a cross-sectional survey of sodium removal in unselected patients on CAPD and APD; study B was a prospective study of 32 CAPD patients who were about to be changed to APD (sodium removal was measured before and after the change); and study C comprised 16 patients (10 on CAPD, 6 on APD) who were on icodextrin for the long dwell. For any magnitude of ultrafiltration, sodium removal was higher in CAPD patients than in APD patients. Nine of 17 CAPD patients and 47 of 51 APD patients with daily ultrafiltration < 1 L had a daily sodium removal by PD of < 100 mmol/L (p < 0.001). Multivariate analysis showed that the two main determinants of peritoneal sodium removal were ultrafiltration and the mode of PD. Sodium removal was markedly higher in CAPD. As expected, diuresis was positively and independently associated with total sodium removal. The authors concluded that standard APD schedules are frequently associated with poor sodium removal rates and that ultrafiltration can be used as a surrogate for sodium removal in CAPD, but not in APD (4). Those findings have important clinical implications because, over the last few years, the number of patients on APD has been steadily increasing.
**Cardiovascular factors that influence mortality**

**LEFT VENTRICULAR HYPERTROPHY**

Left ventricular hypertrophy is common among pre-dialysis and ESRD patients. The presence of LVH is an important and independent risk factor for mortality in ESRD patients (29).

Although earlier reports indicated that LVH regresses after initiation of CAPD (24), recent studies point to the contrary. Left ventricular hypertrophy is evident in long-term CAPD patients. Takeda et al. (30) compared patients on long-term CAPD, short-term CAPD, HD (no diabetes), and HD (with diabetes) with controls and found that the left ventricular mass index (LVMI) and the ratio of the peak atrial filling velocity to the peak diastolic flow velocity were greatest in long-term CAPD (166.4 ± 84.3 g/m² and 1.25 ± 0.4 respectively). Meanwhile, left ventricular fractional shortening (%FS) was smallest (34% ± 10.8%) among the long-term CAPD patients (30). Enia et al. (8) found that LVH was present in 86% of CAPD patients as compared with 62% of HD patients. The LVMI was higher in CAPD patients than in HD patients (133 ± 39 g/m² vs. 157 ± 37 g/m²). In another study, Eisenberg et al. (31) followed 21 CAPD patients for 18 months. The initial prevalence of LVH was 52%; it later increased to 76%. The mortality in patients with moderate and severe LVH was 25% and 56% respectively.

Interestingly, Wang et al. (32) recently reported a novel association between RRF and LVH in PD patients. They performed a cross-sectional study of 158 non diabetic CAPD patients. Using echocardiography, they determined LVMI and its relationship with residual glomerular filtration rate (GFR), PD, total weekly urea clearance (Kt/V), and other known risk factors for LVH. Twelve patients had no LVH (group I). The remaining 146 patients were stratified according to their LVMI (median: 207 g/m²; range: 103 – 512 g/m²), from group II (lowest), through group III, to group IV (highest). Across the four groups of patients with increasing LVMI, a significant decline in GFR (group I: 2.27 ± 1.98 mL/min/1.73 m²; group II: 1.49 ± 1.58 mL/min/1.73 m²; group III: 1.61 ± 1.91 mL/min/1.73 m²; group IV: 0.80 ± 1.42 mL/min/1.73 m²; p = 0.011) and total weekly Kt/V (group I: 1.98 ± 0.44; group II: 1.96 ± 0.38; group III: 1.92 ± 0.42; group IV: 1.71 ± 0.42; p = 0.037) were seen; however, the PD Kt/V was similar for all four groups. Patients with better-preserved residual GFR not only had significantly higher total Kt/V, but were less anemic and hypoalbuminemic and showed a trend toward lower systolic blood pressure and arterial pulse pressure. Multiple regression analysis showed that residual GFR was independently associated with LVMI. The authors concluded that prospective studies are needed to determine if a cause–effect relationship indeed exists; to evaluate if a decline in residual GFR is independently associated with an increase in LVMI; and to determine whether treatment directed at preserving RRF will reduce the severity of LVH and improve cardiac performance and, hence, the survival of patients.

Silaruks et al. (33) studied the clinical outcome of LVH (LV wall diastole thickness ⊕ 1.2 cm) detected by echocardiography in non diabetic CAPD patients without dilated cardiomyopathy. Of 66 patients, 20 had a normal echocardiogram (LV wall thickness < 1.2 cm), 21 had mild hypertrophy, and 25 had severe hypertrophy (LV wall thickness > 1.4 cm in diastole). In the first two groups, 21% were admitted with congestive heart failure (CHF) after starting dialysis. The 1-year cumulative survival was 85% among those with mild hypertrophy and 91% in the normal group. In the group with severe hypertrophy, 57% were admitted at least once with CHF, and the 1-year cumulative survival was 56%. Among those who died in the severe group, the 82% who died from cardiac or cerebrovascular causes accounted for the significantly worse survival (p = 0.003) in that group as compared with the 0% of patients who died from those causes in the group with a normal echocardiogram. The authors concluded that severe LVH was found in a third of CAPD patients and was associated with a significantly high cardiovascular morbidity and mortality (33).

**Sodium removal, BP, fluid control, and mortality**

Recently, sodium and fluid removal were shown to be associated not only with better BP control but also with improved survival. Ates et al. studied 125 PD patients (116 on CAPD, 9 on APD) and followed them for 3 years (34). The patients were classified according to sodium removal during the follow-up period. In group I, total sodium removal was below the 25th percentile value (<130 mmol/1.73 m² in 24 hours); in group II, total sodium removal was between the 25th and 50th percentile value (131 – 180 mmol/1.73 m² in 24 hours); in group III, total
sodium removal was between the 50th and 75th percentile value (181 – 232 mmol/1.73 m² in 24 hours); and in group IV, total sodium removal was above the 75th percentile value (>232 mmol/1.73 m² in 24 hours). The 3-year survival rates were significantly different among the groups (group I: 59.3%; group II: 73.1%; group III: 88.9%; group IV: 96.1%; \( p < 0.01 \); Figure 2). Similarly, patients were classified into four groups according to mean fluid removal. The 3-year survival rates were significantly different among those groups, too (group I: 61.5%; group II: 71.4%; group III: 88.0%; group IV: 96.3%; \( p < 0.01 \); Figure 3). Total sodium removal was found to be negatively correlated with systolic and diastolic BP levels and with the use of antihypertensive drugs. The authors also noted a statistically significant correlation between total fluid removal and both systolic and diastolic blood pressure. Using the Cox proportional hazards model, they estimated that a change of 10 mmol/1.73 m² more in total sodium removal in 24 hours, and a change of 100 mL/1.73 m² more in total fluid removal in 24 hours was associated with a 10% decrease in relative risk (RR) of death.

Recently, the EAPOS (European APD outcome study group) performed a prospective multicentric study involving 174 anuric patients on APD to determine APD feasibility and outcomes (35). The authors found that age above 65 years predicted worse patient survival (65% vs. 86%, \( p = 0.001 \)) and baseline ultrafiltration \( \geq 750 \) mL in 24 hours predicted better technique survival (63% vs. 50%, \( p = 0.004 \)) and probably better patient survival (83% vs. 67%, \( p = 0.007 \)). Interestingly, baseline creatinine clearance and D/P had no effect on patient or technique survival.

Those findings have important implications for the long-term PD patient. Dialysis adequacy should not be based on a specific value of weekly creatinine clearance or \( K_t/V \), but should incorporate other variables such as BP control and normovolemia. In other words, dialysis is inadequate if a patient achieves a particular target for solute clearance but has poor BP control or excessive volume expansion (or both).

**Conclusion**

Recognition is increasing that, because of volume overload and poor BP control, PD patients are probably at higher risk for adverse cardiovascular events as compared with HD patients. The underlying pathogenesis is loss of RRF or ultrafiltration failure (or both). Continued salt intake in the presence of declining RRF further worsens the situation. Recently, APD patients have been shown to have poor sodium removal rates as compared with CAPD patients. That observation needs to be confirmed in larger studies.
because the use of APD as a mode of treatment for ESRD is rapidly increasing. Better BP and volume control would probably increase the long-term survival of PD patients.

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