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Fluid overload as a major target in management of cardiorenal syndrome: Implications for the practice of peritoneal dialysis

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Abstract

Congestion is an integral component of cardiorenal syndrome and portends an adverse impact on the outcomes. Recent studies suggest that congestion has the ability of

modulating the interactions between the kidney and the heart in this setting. Peritoneal dialysis (PD) is a home-based therapeutic modality that is not only offered to patients with end-stage renal disease to provide solute clearance and ultrafiltration, but it has also been used in patients with refractory heart failure and fluid overload to help optimize volume status. Several uncontrolled studies and case series have so far evaluated the role of PD in management of hypervolemia for patients with heart failure. They have generally reported favorable results in this setting. However, the data on the outcomes of patients with end-stage renal disease and concomitant heart failure is mixed, and the proposed theoretical advantages of PD might not translate into improved clinical endpoints. Congestion is prevalent in this patient population and has a significant effect on their survival. As studies suggest that a significant subset of patients with end-stage renal disease who receive PD therapy are hypervolemic, suboptimal management of congestion could at least in part explain these conflicting results. PD is a highly flexible therapeutic modality and the choice of techniques, regimens, and solutions can affect its ability for optimization of fluid status. This article provides an overview of the currently available data on the role and clinical relevance of congestion in patients with cardiorenal syndrome and reviews potential options to enhance decongestion in these patients.

Key words: Heart failure; Peritoneal dialysis; Congestion; Cardiorenal syndrome

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Core tip: Congestion has been recognized as a dynamic state capable of modulating the interactions between the heart and the kidney in patients with cardiorenal syndrome. Optimization of volume status could significantly affect the outcomes of patients treated with peritoneal dialysis (PD) patients for end-stage renal disease and

pre-existing heart failure. Since PD is a highly modifiable therapeutic modality, it is conceivable that a regimen customized to the clinical characteristics and needs of the patients could improve their outcomes through efficient decongestion and optimization of volume status.

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INTRODUCTION

Heart failure (HF) is a public health problem due to its increasing prevalence, associated morbidity, high mortality, and a remarkable financial burden on the healthcare system. Prevalence of HF increases with age; it is currently one of the most common chronic conditions with a lifetime prevalence reaching 20%-33% in the United States^[1]. Despite advancements in diagnosis and treatment, the HF population is expected to expand to more than 8 million by 2030 due to the increase in the proportion of aging population as well as the improving number of patients surviving ischemic events^[2].

Congestion is the hallmark of HF, is the primary reason for hospitalization of these patients, and can contribute to HF progression^[3]. Renal dysfunction is a prevalent clinical finding in HF and portends an untoward impact on potential management options, course, and outcome. The population of patients presenting with both heart failure and chronic kidney disease [*i.e.*, cardiorenal syndrome (CRS)] is large and steadily growing^[3,4]. The pathophysiology of HF is complex as there exist a multitude of mechanisms by which the heart and the kidneys interact in the setting of cardiac dysfunction. Congestion can directly affect the interactions between the kidney and the heart in CRS^[4]. Indeed, several studies have so far highlighted the clinical significance of congestion, rather than renal dysfunction, as the primary driver of the adverse outcomes in patients with CRS. For example, in a study on 594 patients with acute HF, patients with concomitant congestion and deterioration in renal function had the worst outcomes while worsening kidney function alone (without lingering congestion) showed no adverse impact^[5]. Similarly, in a study on HF patients who were admitted to the hospital for congestion, those with hemoconcentration (proxy for decongestion) presented more often with deterioration in renal function but their outcome (*i.e.*, time to death) was still significantly improved compared to those who did not experience hemoconcentration during their hospitalization^[6].

FLUID OVERLOAD IN CRS

In chronic CRS, the maladaptive mechanisms involved in HF, whether in the form of low forward flow or high backward pressure, could ultimately result in diminished water and sodium excretion, lingering venous congestion, endothelial cell activation, systemic inflammation, and progressive deterioration in renal function to the point of renal failure and end-stage renal disease (ESRD)^[7]. In a subset of patients with HF, reduced cardiac output and fluid redistribution result in decreased renal perfusion. The aberrant compensatory mechanisms such as activation of the sympathetic nervous system, renin-angiotensin-aldosterone axis, and arginine vasopressin lead to enhanced renal water and sodium absorption in an effort to preserve renal perfusion, transglomerular pressure, and glomerular filtration rate. However, at long term, these mechanisms could induce deleterious effects on the heart and the kidney by promoting fibrosis, apoptosis, oxidative stress, activation of inflammatory mechanisms, and ventricular remodeling^[8,9]. A number of studies have also found an association between high venous pressures and deterioration in renal function that could be even stronger than the impact of arterial blood pressure or cardiac index on renal function^[10,11]. Increased pressure along renal veins is thought to reduce the net pressure gradient across the glomerulus leading to a decrease in glomerular filtration rate, diminished renal excretion of water and sodium, and progressively worsening congestion^[10].

Hence, systemic congestion is a key target in management of these patients, and its relief is considered a treatment success. Control of congestion not only is associated with improvement in clinical outcomes and reduction in the rate of hospitalization, but could also prevent progression of kidney disease associated with renal venous congestion^[12].

While high dose intravenous diuretics remain the cornerstone of decongestive therapy in patients with acute HF and acute CRS, extracorporeal ultrafiltration has recently re-emerged as a potential alternative in this setting with a number of proposed advantages such as effective and predictable fluid removal, efficient sodium extraction, and reduction in the rate of re-hospitalization^[13,14]. In the setting of chronic CRS, the studies have mainly focused on improving cardiac function, whether through medications or devices. The currently available pharmacologic options for decongestion are limited to diuretics that have been in use for several decades as well as the newly marketed neprilysin inhibitors^[15]. However, the use of diuretics in HF remains largely empirical, with potential disadvantages and untoward effects such as variable dose-response rate and diuretic resistance^[16]. Moreover, a number of practical aspects of their use such as concomitant administration of loop and distal diuretics

remain elusive, and an association between high doses of loop diuretics and adverse outcomes has also been proposed by observational studies^[17].

Peritoneal dialysis (PD) represents an intriguing home-based therapeutic option that provides the possibility of continuous, gentle, and customized removal of excess fluid and sodium in patients with HF who commonly present with various degrees of renal dysfunction. Herein, we explore the studies on the role of PD in management of CRS in two subsets of CRS patients separately; those non-ESRD patients with concomitant HF and chronic kidney disease (CKD) in whom PD is primarily used as an ultrafiltration modality for relief of refractory congestion rather than solute clearance, and those patients with HF and concomitant ESRD who have selected PD as a modality for chronic renal replacement therapy.

CKD and HF

Several studies so far have evaluated the role of PD in patients with chronic CRS and refractory volume overload in whom renal dysfunction is not severe enough to necessitate dialysis therapy for clearance of solutes. These trials have in general reported favorable outcomes. In a prospective single-center study including 118 patients with severe HF [New York Heart Association (NYHA) class III and IV], Koch *et al*^[18] evaluated the impact of intermittent automated PD (APD) therapy performed at least three times per week for 12 h per session. Mean baseline creatinine clearance was 19.2 mL/min and the patients were followed for slightly more than a year. The clinical symptoms of HF improved after starting PD as evidenced by improvement in the NYHA class at 6 mo, and fluid overload was also significantly reduced as shown by reduction in body weight from 78.7 to 74.7 kg ($P < 0.001$). In another prospective study, PD therapy was used for management of 25 patients with HF (NYHA class III/IV), CKD, persistent fluid overload, and at least two previous hospitalizations for acute HF^[19]. The mean daily peritoneal ultrafiltration was 679 mL; PD was associated with significant improvement in the Minnesota Living With Heart Failure Questionnaire and NYHA class at 6 and 24 wk. An 84% reduction in the number of hospitalized days for acute HF was also observed. Later, Courivaud *et al*^[20] published the largest study to-date in this field that included 126 patients with refractory HF. The mean estimated glomerular filtration rate was 33.5 mL/min per 1.73 m² and the mean duration on PD was 16 mo. During the first year of PD therapy, left ventricular ejection fraction improved significantly (38% at baseline vs 42% at 1 year, $P = 0.001$). The striking observation of the study was that PD therapy was associated with a 90% reduction in the duration of HF-related hospitalization (3.3 d/patient-month before PD vs 0.3 d/patient-month after PD, $P < 0.0001$). Recently, a meta-analysis of the studies on the use of PD in refractory HF reported that PD was associated with a significant decline in hospitalization

days and improvement in cardiac function defined by left ventricular ejection fraction and NYHA class^[21]. Since congestion is the primary reason for hospitalization of patients with HF, the improvement in the hospitalization of these patients implies better management of fluid overload by PD. It can also have an important impact on the cost related to inpatient care of these patients. Overall, the currently available data suggest that PD is a clinically-relevant therapeutic option for removal of fluid in patients with chronic CRS who present with persistent congestion despite optimal medical therapy. Finally, it is notable that the favorable results of these studies are evident despite typical use of PD as the “last resort” for patients refractory to conventional therapies.

The studies on the role of PD in chronic CRS have three major limitations: Lack of a reasonably matched control group, relatively short follow-up periods, and the possibility of a publication bias. A major concern regarding the use of PD in this patient population has long been that its morbidity might replace that of HF. In modern practice, with an acceptably low incidence of PD-related complications, this concern appears to be less relevant. Moreover, those studies that assessed the quality of life of the patients reported significant improvement after initiation of PD^[22]. Concerning the impact on survival, there is no conclusive evidence to this date to suggest that PD could indeed alter the natural course of the disease state although there have been reports of improvement in cardiac function^[20].

ESRD and HF

For those CRS patients in whom renal dysfunction progresses to ESRD, fluid removal can be achieved through either hemodialysis (extracorporeal ultrafiltration) or PD (intracorporeal ultrafiltration). A number of advantages have been proposed for PD in this setting such as gentle and continuous fluid and solute removal being less likely to exacerbate neurohormonal activation as well as better preservation of residual renal function^[23-25]. Importantly, it has been shown that patients undergoing fluid removal by hemodialysis experience myocardial stunning (*i.e.*, persistent left ventricular dysfunction due to repeated transient demand myocardial ischemia) even in the absence of angiographically significant coronary artery disease^[26]. Myocardial stunning at long run can lead to progression of HF *via* development of fixed systolic dysfunction^[27]. It has been shown that PD is not associated with myocardial stunning and hence would be less likely to lead to progression of HF in ESRD patients^[28].

Despite theoretical advantages of PD therapy in patients with ESRD and HF, studies have so far yielded conflicting results. Panday *et al*^[29] retrospectively compared the outcomes of 139 ESRD patients with concomitant HF, and reported no difference in 2-year mortality, cardiac outcomes, or hospitalization between PD and hemodialysis. Two large registry-based studies on ESRD population (one from United States and one from France) found that PD can be associated

with an even increased risk of mortality compared to hemodialysis in HF patients while these two modalities are associated with similar outcomes in ESRD patients without HF^[30,31]. Similarly, in a study on National Health Insurance Research Database in Taiwan including more than 35000 patients, Wang *et al*^[32] reported that PD was associated with inferior survival in ESRD patients with concomitant HF. It is not clear whether these findings are related to unexplored underlying mechanisms, the interplay of a number of well-known factors [e.g., difficulty in management of volume status in ESRD patients with reduced residual renal function (RRF)], or could possibly reflect the inherent limitations of the registry-based data analysis (e.g., treatment-by-indication bias). On the other hand, in a registry study from Lombardy in Italy, Locatelli *et al.* reported that the risk of *de novo* cardiovascular disease (HF and coronary artery disease) was similar between hemodialysis and PD^[33]. More recently, a study based on Taiwanese national registry including more than 45000 patients with ESRD found that the risk of *de novo* HF in patients receiving hemodialysis is 29% higher than those undergoing PD therapy (CI: 1.13-1.47, $P < 0.001$) although the advantage seemed to disappear over time^[34,35].

Despite the fact that the data is mixed, altogether they imply that the impact of PD as a dialysis modality on the outcomes of ESRD patients with “pre-existing HF” might be different from those without HF.

VOLUME STATUS IN ESRD - FOCUS ON PD

Fluid overload is a prevalent finding in patients with renal dysfunction and is associated with adverse cardiovascular outcomes^[36,37]. Recently, a multicenter study on more than 1000 incident PD patients revealed that fluid overload is present already at baseline when they start PD therapy^[38]. Using bioimpedance spectroscopy, the investigators found that the median fluid overload was 2 L, and less than half of the patients (38.7%) were indeed euvoletic; 25.1% of the patient population also had HF. Unfortunately, initiation of PD therapy does not seem to markedly improve fluid overload in patients with ESRD; congestion appears to remain a prevalent problem in a subset of PD population. For example, in the multicenter cross sectional European Body Composition Monitoring (EuroBCM) study that included 639 patients receiving PD therapy (mean time on PD 32.6 mo), only 40% were found to be euvoletic^[39]. Extracellular fluid volume expansion in PD patients has been shown to be directly associated with increase in inflammatory markers, an established underlying mechanism for deterioration in cardiac function^[40,41]. This could in part explain the unexpected outcomes of ESRD patients with pre-existing HF who choose PD for renal replacement therapy.

In recent years, there has been a renewed interest in the concept of optimization of fluid status in patients receiving renal replacement therapy due to the recognition of its significant impact on survival^[42,43]. Overhydration is associated with hypertension, left ventricular hypertrophy, and increased mortality in PD patients^[44]. Moreover, high serum levels of pro-B type natriuretic peptide (BNP), a surrogate for fluid overload, is an independent predictor of mortality in these patients^[45]. To examine whether fluid overload *per se* is associated with poor outcomes in PD population or it merely reflects potential untoward effects of other comorbidities such as HF, Jotterand Drepper *et al*^[46] studied 54 prevalent PD patients and found that overhydration was a strong and independent predictor of mortality after adjustment for cardiac function (relative hazard of 7.8). Similarly, in a study on 529 PD patients, O'Lone *et al*^[47] found that overhydration measured by bioimpedance spectroscopy is an independent predictor of mortality.

HYDRATION STATUS AND RESIDUAL RENAL FUNCTION

Since RRF has been reported to be associated with reduced mortality in PD patients, preservation of RRF has become one of the major goals in management of patients receiving PD therapy^[48]. The apparent importance of RRF is likely a proxy for adequate volume control in these patients. Since intravascular volume depletion could lead to a loss of RRF, it has been suggested that PD patients should avoid intravascular volume depletion and preferably be maintained hypervolemic to help preserve RRF. However, in an interesting study on 237 ESRD patients, McCafferty *et al*^[49] showed that extracellular volume expansion measured by bioimpedance did not have any association with preservation of RRF. Moreover, correction of severe overhydration does not seem to result in a significant drop in RRF^[50]. Therefore, based on currently available data, overhydration in the setting of PD therapy could increase the risk of cardiac dysfunction and adverse outcomes without an apparent beneficial impact on preservation of RRF.

VOLUME STATUS VS SOLUTE CLEARANCE

The clinical relevance of fluid overload and its impact on the outcomes in the setting of PD is to the point that euvoemia is likely to be even more important than small solute clearance as a marker of dialysis adequacy because fluid overload, but not small solute clearance, could predict outcomes^[45,51]. In the landmark Canada-United States study that included 601 PD patients, urine volume superseded renal small solute clearance as a predictor of mortality; every 250 mL increment in urine

volume was associated with a 36% reduction in the risk of death^[48]. In an interesting study on 125 PD patients, Ateş *et al*^[52] showed that total sodium and fluid removal were independent factors affecting survival while Kt/V_{urea} and total creatinine clearance were not. Similarly, in the European Automated Peritoneal Dialysis Outcome Study, the survival of 177 anuric patients who were treated with PD was associated with baseline ultrafiltration, but not with clearance of creatinine or membrane permeability status^[53].

DECONGESTION: SODIUM VS WATER

The common pathway for several maladaptive mechanisms involved in the development of HF is aberrancy in renal excretion of sodium with resultant extracellular fluid expansion. Since sodium is the main determinant of extracellular fluid volume, any therapeutic modality with greater ability for extraction of sodium will be advantageous in the setting of HF and volume overload. In a landmark study on vasopressin antagonists, addition of a vasopressin receptor antagonist to standard therapy of HF (with subsequent enhanced sodium-free water excretion) failed to reduce all-cause mortality, cardiovascular death, or re-hospitalization despite significant decongestion, highlighting the paramount role of sodium removal in this setting^[54]. When applying therapeutic modalities for management of fluid overload, this distinction should be taken into consideration. In the PD therapy, during the first 60–90 min of the intraperitoneal dwell of the dextrose-containing PD solution, rapid transport of solute-free water takes place across the aquaporins while the remaining solute-rich water moves much more slowly through the small pores of the peritoneal membrane. Hence, the initial dissociation between the rate of water and sodium transport into the peritoneal cavity results in an early drop in the concentration of dialysate sodium, called sodium sieving. The slow diffusive movement of sodium continues and, if the dwell is long enough, the concentration of sodium in the dialysate will eventually approach that of serum. These mechanistic considerations should be accounted for when PD therapy is offered to ESRD patients with HF as there seem to be significant variations in the ability of this therapy for fluid and sodium removal based on the techniques as well as the regimens that are selected.

DECONGESTION: CAPD VS APD

The concept of sodium sieving is clinically relevant in that shorter dwells, such as those typically achieved with APD, might not provide enough time for adequate extraction of sodium; they could mainly result in removal of sodium-free water and lead to reduced net sodium removal and progressive congestion at long run. Longer dwells, such as those typically provided by continuous ambulatory peritoneal dialysis (CAPD), might be advantageous in the setting where sodium

removal is the primary target (*i.e.*, patients with HF and volume overload). In a study on 141 PD patients, sodium removal was found to be significantly greater in those receiving CAPD compared to APD group, and switching techniques from CAPD to APD led to significant reduction in sodium removal^[55]. In another study, BNP (a surrogate for volume status) and left ventricular mass were reported to be significantly higher in the APD patients compared with CAPD^[56]. It should however be noted that several other factors such as the PD solutions and the regimens as well as the clinical characteristics and dietary habits of the patients can affect these results. For example, in a study on 158 prevalent PD patients (90 CAPD, 68 APD), Davison *et al*^[57] used bioimpedance spectroscopy to assess and compare the hydration status of the patients. They reported no difference between APD and CAPD with regard to the ratio of extracellular fluid volume to total body water. Mean total daily removal of sodium was 109 mmol for patients on CAPD and 130 mmol for APD ($P = 0.23$). Among CAPD patients, 41% had a sodium removal of less than 100 mmol/d compared to 33.8% in the APD group ($P = 0.36$). Blood pressure was also similar in the two groups. The results of this study can be in part explained by the fact that nearly 80% of the APD patients were on icodextrin for their long daytime dwell (hence improving fluid management), and also the number of nocturnal exchanges were decreased (*i.e.*, allowing for longer dwells and less sodium sieving).

ENHANCING SODIUM REMOVAL

Since sodium concentration of most conventional PD solutions (*i.e.*, 132 mmol/L) is close to that of serum, sodium removal is mainly convective; diffusion does not typically play an important role in this setting. In an attempt to improve sodium extraction through increased diffusion gradient, a number of studies have evaluated the impact of low-sodium PD solutions on various endpoints. For example, in a recent randomized controlled trial on 108 patients, Rutkowski *et al*^[58] used PD solution containing 125 mmol/L of sodium and compared it with the control group. They found that low-sodium solution could significantly increase sodium removal (by 1.1 g/d, $P < 0.001$) and improve blood pressure control. Although low-sodium solutions can prove helpful in specific settings and select patients (*i.e.*, those with HF), their widespread use is hindered by a number of factors such as reduced osmolality of the solution and consequent decrease in ultrafiltration thus offsetting their benefit.

APD, once used mainly for patients who were rapid transporters, has become the modality of choice by many patients and physicians in the developed countries due to it being not only convenient and adaptable to the lifestyle of patients but also modifiable to fit a wide range of clinical characteristics and needs. In the United States, more than 70% of patients are treated with this technique^[59]. As previously mentioned,

there is concern with regard to the ability of APD to adequately extract sodium and to address congestion in these patients. There are a number of strategies that are based on the mechanisms of water and solute transport in PD and can potentially improve fluid and sodium extraction by APD. This could be of special importance in specific clinical settings such as HF where decongestion, rather than clearance, is the primary target of this therapy. Decreasing the number of nocturnal cycles could increase the dwell time hence reducing sodium sieving. This is likely to improve sodium removal and, if the patient is on low sodium diet, could provide negative or even sodium balance especially through concomitant use of loop diuretics for those with significant RRF. Adding an exchange in the evening for select APD patients (*i.e.*, those with slow peritoneal transport characteristics) could also ensure adequate small solute clearance while further increasing sodium removal. Use of icodextrin, a high molecular weight glucose polymer developed specifically for use as an alternative osmotic agent to dextrose during the once-daily long-dwell exchange, allows for sustained fluid removal and optimization of volume status due to reduced back diffusion^[60]. Icodextrin has the advantage that it does not activate aquaporins; all the ultrafiltration takes place at the intercellular small pores where sodium fluxes with water (*i.e.*, no sodium sieving). This process allows for more efficient sodium removal compared to an equal volume of ultrafiltration with a dextrose-based solution. Therefore, icodextrin could prove helpful in clinical settings such as HF where enhanced sodium removal is of particular importance. In a multicenter randomized controlled trial on 50 PD patients with urine volume of less than 750 mL/d and high solute transport, Davies *et al*^[61] reported an average increase of 61.7 mmol in daily sodium removal and an average increase of 399 mL in ultrafiltration in patients receiving icodextrin instead of a glucose-based solution. Basile *et al*^[62] reported their experience with the use of icodextrin (1 to 2 exchanges a night) in patients with end-stage HF and severe volume overload over a follow up period of 2 years. After starting PD, the patients experienced a significant decrease in their mean weight by 11.3 kg ($P < 0.007$), an increase in urine output (from 587 to 1700 mL/d, $P < 0.003$), and significant reduction in the number of days hospitalized for HF (from 4.4 to 0.7 d/mo, $P < 0.04$). Therefore, the initial results with the use of icodextrin seem to be promising. A combination of the above-mentioned strategies (simultaneous or successive) could be used to enhance effective sodium removal by APD and help further improve patients' volume status. Whether these approaches would translate to better outcomes is to be determined by future studies.

CONCLUSION

While lingering congestion remains an unresolved issue in a significant subset of patients with CRS, PD therapy

has been offered as a clinically-relevant alternative to conventional therapies for optimization of volume. In those patients who present with ESRD and pre-existing HF, there is mixed data with regard to the role of PD therapy and its impact on survival. Whether this is related to suboptimal management of overhydration or other factors remains elusive. Optimization of volume status appears to be at least as important as providing clearance in patients receiving PD therapy, and sodium removal plays an integral role in this regard especially in those with concomitant HF. Clinicians could take advantage of the known strategies to enhance extraction of sodium-rich effluent in these patients. Future studies are needed to assess whether these methods would indeed lead to improvement of the outcomes.

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