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MINIREVIEWS

Peritoneal dialysis for chronic cardiorenal syndrome: Lessons learned from ultrafiltration trials

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Abstract

The current models of cardiorenal syndrome (CRS) are mainly based on a cardiocentric approach; they assume that worsening renal function is an adverse consequence of the decline in cardiac function rather than a separate and independent pathologic phenomenon. If this assumption were true, then mechanical extraction of fluid (*i.e.*, ultrafiltration therapy) would be expected to portend positive impact on renal hemodynamics and function through improvement in cardio-circulatory physiology and reduction in neurohormonal activation. However, currently available ultrafiltration trials, whether in acute heart failure (AHF) or in CRS, have so far failed to show any improvement in renal function; they have reported no impact or even observed adverse renal outcomes in this setting. Moreover, the presence or absence of renal dysfunction seems to affect the overall safety and efficacy of ultrafiltration therapy in AHF. This manuscript briefly reviews cardiorenal physiology in AHF and concludes that therapeutic options for CRS should not only target cardio-circulatory status of the patients, but they need to also have the ability of addressing the adverse homeostatic consequences of the associated decline in renal function. Peritoneal dialysis (PD) can be such an option for the chronic cases of CRS as it has been shown to provide efficient intracorporeal ultrafiltration and sodium extraction in volume overloaded patients while concurrently correcting the metabolic consequences of diminished renal function. Currently available trials on PD in heart failure have shown the safety and efficacy of this therapeutic modality for patients with chronic CRS and suggest that it could represent a pathophysiologically and conceptually relevant option in this setting.

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

Core tip: This article briefly reviews the clinical significance of renal dysfunction in heart failure and evaluates the results of the ultrafiltration studies in acute heart failure and cardiorenal syndrome (CRS). It concludes that peritoneal dialysis could represent an

efficacious option for chronic CRS due to its ability to simultaneously address renal and cardiac dysfunction in these patients. Recent technical advances such as possibility of initiating peritoneal dialysis (PD) in the acute setting and placement of the PD catheter by interventional radiology could make this home-based therapeutic option even more accessible and intriguing.

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INTRODUCTION

Renal dysfunction is a prevalent feature of heart failure (HF) and portends adverse impact on its potential management options, course, and outcomes. Although several therapeutic strategies have so far been evaluated for patients who present with simultaneous dysfunction of the heart and the kidney [*i.e.,* cardiorenal syndrome (CRS)], the optimal therapy for "chronic" CRS remains largely unknown. This could reflect the paucity of data on the precise mechanisms underlying this syndrome, which is unfortunately unlikely to resolve soon due to its complexity. The contemporary question for clinicians providing care for patients with chronic CRS is whether there exists a safe management strategy that could provide this group of patients with improved outcomes and quality of life compared with conventional therapies. The answer might paradoxically lie in the lessons learned from trials on "acute heart failure" (AHF).

ULTRAFILTRATION FOR HF AND CRS

In the last decade a multitude of attempts have been aimed at finding more efficacious and safer therapies for AHF[1]. While trials on pharmacologic agents such as endothelin receptor antagonists and adenosine receptor antagonists have mostly been disappointing, extracorporeal ultrafiltration has shown promising results that ranged from more efficient fluid and sodium removal to reduction in the rate of re-admission[2,3]. Indeed, ultrafiltration has been recognized as an emerging therapy for patients with AHF which can be used either as an alternative to conventional diuretic-based strategies or as an adjuvant therapy. However, it is noteworthy that patients with significant renal dysfunction have often been excluded from the ultrafiltration trials and as such their favorable results can hardly be extrapolated to common clinical scenarios in which the decline in renal function parallels deterioration in cardiac status[3,4].

In contrast to most previous AHF studies, the recently published Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome (CARRESS-HF) trial examined the role of ultrafiltration in management of patients with AHF who also presented with worsening renal function (WRF)[5]. In this randomized controlled trial that included 188 patients, ultrafiltration was compared to a diuretic-based pharmacologic therapy in patients who were admitted with a primary diagnosis of AHF and experienced acute CRS. Surprisingly, once the renal component was added to the clinical picture, the favorable findings of the previous trials were not observed anymore; ultrafiltration was found to be inferior to pharmacologic therapy with regards to its impact on both renal function and development of serious adverse events, and the recruitment of the patients had to be stopped. Although considered a trial of AHF, the unprecedented design of CARRESS-HF (*e.g.*, inclusion of patients with an increase in serum creatinine level as small as 0.3 mg/dL up to 3 mo prior to admission to the hospital) made it possible for the trial to also recruit and follow patients with cardiorenal physiology of less acuity.

CARDIO-RENAL PHYSIOLOGY AND ULTRAFILTRATION

Renal dysfunction is an established predictor of adverse outcomes in patients with HF. Until recently, the traditional model of therapy for HF mainly focused on low cardiac output (*i.e.*, low forward flow) being the trigger for a cascade of pathologic events ultimately leading to deterioration in renal function. Even though most patients admitted for AHF present with normal blood pressure, a significant subset still experience concomitant WRF and CRS. Therefore, the decrease in renal perfusion pressure secondary to reduced stroke volume, which was once considered the major mechanism, cannot fully explain renal dysfunction of all these patients. Indeed, more recent data suggested that WRF in the setting of AHF would correlate better with the degree of renal venous congestion rather than cardiac output (*i.e.*, high backward pressure)[6]. In this model, alteration in renal function is more related to right atrial and central venous pressure than cardiac index or left ventricular ejection fraction, hence proposing the hypothesis of backward rather than forward failure.

Does ultrafiltration therapy affect cardiac physiology and hemodynamic status? A number of studies including those using invasive methods have reported several beneficial effects on cardio-circulatory parameters such as cardiac index and systemic vascular resistance following ultrafiltration therapy. While the precise mechanisms remain to be determined, these positive results could still be explained to some extent by the aforementioned models of CRS. On the arterial side, efficient fluid removal by ultrafiltration therapy reduces left ventricular end-diastolic volume and pushes the heart towards the left side of the Frank-Starling curve.

Table 1 Proposed benefits of peritoneal dialysis therapy for heart failure

Continuous gentle ultrafiltration with minimal impact on hemodynamic status
Improvement in functional status and symptoms of volume overload
Reduction in number of days of heart failure-related hospitalizations
Restoration of diuretic responsiveness
Reduction in weight and improvement in volume status
Improvement in left ventricular ejection fraction
Sodium sieving effect and possibility of better control of natremia
Removal of pro-inflammatory mediators (medium-sized molecules)
Reduction in intra-abdominal pressure in patients with severe ascites
Improvement in quality of life
Improved atherogenic lipid serum profile
Lack of impact on neurohormonal activity (renin-angiotensin-aldosterone system and sympathetic nervous system)
Improved control of serum potassium level (hence providing the opportunity to use medications such as aldosterone receptor blockers)
Reduction in healthcare cost

Adapted from Courivaud *et al*[9], with permission.

This effect can hinder the intermediary pathways such as activation of renin-angiotensin-aldosterone and sympathetic nervous systems and their downstream adverse effects such as ventricular remodeling and perturbation in renal hemodynamics. On the right side, ultrafiltration extracts fluid directly and exclusively from the venous side of the circulation leading to immediate reduction in preload, ventricular wall stress, and capillary hydrostatic pressure. Decongestion of the venous side of the circulation has also been reported to improve renal vein engorgement without affecting counteracting intermediate pathways such as adenosine receptors and tubuloglomerular feedback that result in a decrease in glomerular filtration rate. We have previously reviewed the currently available data on the interactions between the cardiocirculatory system and the kidney in the setting of AHF, and the potential role of ultrafiltration in modifying these mechanisms[7].

RENAL IMPLICATIONS OF ULTRAFILTRATION TRIALS

The common theme in the above-mentioned models of CRS is the dependence of the renal component on the cardiac status (*i.e.*, a cardiocentric approach). They both assume that WRF is an adverse consequence of the decline in cardiac function rather than a separate and independent phenomenon. If this assumption were true, then ultrafiltration therapy would be expected to portend positive impact on renal hemodynamics and function as it is capable of improving cardio-circulatory physiology and reducing neurohormonal activation. However, available ultrafiltration trials, whether in AHF alone or in CRS, have so far failed to show any improvement in the associated WRF; they have either reported no impact or even observed adverse renal outcomes in this setting[3,5]. This important observation questions the accuracy of the above-mentioned cardiocentric models of WRF in AHF, and suggests that renal component of acute CRS is not merely a consequence of deterioration in cardio-circulatory status or the use of conventional therapies in a subset of patients; it can reflect an independent but related phenomenon that needs to be regarded and managed separately. In this model, a number of maladaptive mechanisms (*e.g.*, inflammation and endothelial cell dysfunction) are shared by the kidney and the heart resulting in a decline in the function of both organs and development of CRS. As such, any therapeutic option for this syndrome should not only target cardio-circulatory status, but it also needs to have the ability of addressing the adverse homeostatic consequences of the decline in renal function. In this respect, ultrafiltration might not be the optimal option for management of all cases of acute CRS, as supported by recent trials such as CARRESS-HF, simply due to the fact that it lacks any clearance property and cannot address the diverse metabolic and homeostatic derangements associated with concomitant renal dysfunction.

PERITONEAL DIALYSIS AND CHRONIC CRS

In the chronic setting, where patients present with various degrees of HF and slowly declining renal function, a therapy with the ability of simultaneously addressing both organs will be conceptually attractive and mechanistically relevant. Peritoneal dialysis (PD) can be such an option. PD has been shown to provide efficient intracorporeal ultrafiltration and sodium extraction in volume overloaded patients (especially through the use of icodextrin solution), while concurrently correcting the metabolic consequences of diminished renal function. It has also been reported to portend less well-characterized benefits such as removal of myocardial depressant factors and improvement in endothelial dysfunction (Table 1). It is noteworthy that not all proposed beneficial mechanisms are exclusive to PD; while many can be the direct consequences of using this specific therapeutic modality (*e.g.*, reduction in intra-abdominal pressure in patients with severe ascites), some can also be achieved through other methods of renal replacement therapy such as hemodialysis (*e.g.*, reduction in weight and improvement in volume status).

Several uncontrolled PD studies have so far reported favorable results for patients with chronic CRS despite the fact that they often used PD as "the last resort" for very sick patient populations who were refractory to alternative options and were not candidates for heart transplant[8-10]. For instance, in a study on 126 patients with refractory heart failure and various degrees of renal dysfunction, Courivaud *et al*[10] reported a 90% reduction in the number of days of hospitalization after initiation of PD (3.3 d/patient per month *vs* 0.3 d/patient per month; $P < 0.0001$).

Table 2 Selected studies on the role of peritoneal dialysis in heart failure

Ref.	Study design	No. of patients	Mean age (yr)	Male gender	NYHA class	EF	Renal function	Main findings	Comment
Koch *et al*[11]	Prospective	118	73.2	60.2%	Ⅲ (49.2%) Ⅳ (50.8%)	43.5%	Creatinine clearance 19.2 mL/min	Significant improvement in body Weight and NYHA class	Negligible incidence of peritonitis and catheter dysfunction
Núñez *et al*[8]	Prospective	25	75.1	72%	Ⅲ or Ⅳ (100%)	40%	eGFR 33 mL/min per 1.73 m^2	Significant improvement in patients' clinical status and NYHA class	Marked reduction in the number of days hospitalized for acute heart failure
Bertoli *et al*[12]	Multicenter retrospective	48	74	81%	Ⅱ (6%) Ⅲ (48%) Ⅳ (46%)	30%	eGFR 21 mL/min per 1.73 m^2	Significant improvement in NYHA class and reduction in the number of days hospitalized	Significant reduction in pulmonary artery pressure and improvement in EF
Courivaud *et al*[10]	Retrospective	126	72	69%	N/A	38%	eGFR 33.5 mL/min per 1.73 m^2	Significant reduction in the number of days hospitalized for acute heart failure	Improvement in cardiac function in patients with a an EF of 30% or less

NYHA: New York Heart Association.

The results of selected studies on the role of PD in HF are summarized in Table 2. Since HF is the single most common reason for hospitalization of patients over 65 and the majority of its cost is related to the in-hospital care, use of this home-based therapy for chronic CRS could potentially lead to significant savings in healthcare expenditure while providing a better quality of life for patients. The advantages, potential mechanisms, safety, and efficacy of this therapeutic modality for patients with HF has been discussed elsewhere[9]. In patients with significant residual renal function who do not require dialytic support, nocturnal automated PD or a single night time exchange with icodextrin solution could be sufficient to maintain euvolemia. Depending on the severity of HF, degree of volume overload, symptoms, and comorbidities, the PD therapy can be customized and some patients could use it only a few nights a week rather than every night. In patients with more severe renal dysfunction who require dialytic support for clearance, continuous ambulatory PD or automated PD with day time icodextrin exchange could have the greatest promise to generate the needed gentle continuous ultrafiltration while providing adequate clearance.

A major concern regarding the use of PD in this patient population has been that its morbidity might replace the morbidity from HF. This issue seems to be less compelling nowadays with reasonably low incidence of PD-related complications such as peritonitis, catheter dysfunction, and hernias as reported by most studies as well as the reports on the reduction in HF-related hospitalization after initiation of PD. Moreover, although the data are not consistent, it appears that PD does not alter the natural history of the disease and as such is unlikely to have a significant effect on survival of these patients. Finally, it should be noted that the current literature on the use of PD in the setting of HF still suffers from significant limitations which could hamper its more widespread use (*e.g.*, lack of an appropriately matched control group and relatively short follow-up periods). This could explain the fact that despite aforementioned advantages of this modality, PD is not yet considered by the professional cardiology societies as a therapeutic option for HF. Future prospective randomized studies with longer follow-up periods could address the knowledge gap and prove helpful in this regard.

In summary, based on the currently available data, PD represents one of the few options for patients with chronic CRS that not only is pathophysiologically and conceptually relevant, but is also reported to be safe and effective in several clinical trials. Recent technical advances such as possibility of initiating PD in the acute setting and placement of the PD catheter by interventional radiology could make this home-based therapeutic option even more accessible and intriguing[13].

REFERENCES

1 **Kazory A**, Ross EA. Emerging therapies for heart failure: renal mechanisms and effects. *Heart Fail Rev* 2012; **17**: 1-16 [PMID: 20803357 DOI: 10.1007/s10741-010-9191-5]

2 **Kazory A**, Ross EA. Contemporary trends in the pharmacological and extracorporeal management of heart failure: a nephrologic perspective. *Circulation* 2008; **117**: 975-983 [PMID: 18285578 DOI: 10.1161/CIRCULATIONAHA.107.742270]

3 **Costanzo MR**, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, Jaski BE, Fang JC, Feller ED, Haas GJ, Anderson AS, Schollmeyer MP, Sobotka PA. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol* 2007; **49**: 675-683 [PMID: 17291932]

4 **Costanzo MR**, Saltzberg M, O'Sullivan J, Sobotka P. Early ultrafiltration in patients with decompensated heart failure and diuretic resistance. *J Am Coll Cardiol* 2005; **46**: 2047-2051 [PMID: 16325040]

5 **Bart BA**, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, Redfield MM, Deswal A, Rouleau JL, LeWinter MM, Ofili EO,

Stevenson LW, Semigran MJ, Felker GM, Chen HH, Hernandez AF, Anstrom KJ, McNulty SE, Velazquez EJ, Ibarra JC, Mascette AM, Braunwald E. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med* 2012; **367**: 2296-2304 [PMID: 23131078 DOI: 10.1056/NEJMoa1210357]

6 **F Gnanaraj J**, von Haehling S, Anker SD, Raj DS, Radhakrishnan J. The relevance of congestion in the cardio-renal syndrome. *Kidney Int* 2013; **83**: 384-391 [PMID: 23254894 DOI: 10.1038/ki.2012.406]

7 **Marana I**, Marenzi G, Kazory A. Extracorporeal ultrafiltration for heart failure: focus on organ cross talk and clinical trials. *Nephrol Ther* 2014; **10**: 203-209 [PMID: 24997009 DOI: 10.1016/j.nephro.2014.02.006]

8 **Núñez J**, González M, Miñana G, Garcia-Ramón R, Sanchis J, Bodí V, Núñez E, Puchades MJ, Palau P, Merlos P, Llàcer A, Miguel A. Continuous ambulatory peritoneal dialysis as a therapeutic alternative in patients with advanced congestive heart failure. *Eur J Heart Fail* 2012; **14**: 540-548 [PMID: 22327061 DOI: 10.1093/eurjhf/hfs013]

9 **Courivaud C**, Kazory A. Can we treat fluid overload with fluid? Role of peritoneal dialysis in management of heart failure. *Eur J Heart Fail* 2012; **14**: 461-463 [PMID: 22510421 DOI: 10.1093/eurjhf/hfs053]

10 **Courivaud C**, Kazory A, Crépin T, Azar R, Bresson-Vautrin C, Chalopin JM, Ducloux D. Peritoneal dialysis reduces the number of hospitalization days in heart failure patients refractory to diuretics. *Perit Dial Int* 2014; **34**: 100-108 [PMID: 23994842 DOI: 10.3747/pdi.2012.00149]

11 **Koch M**, Haastert B, Kohnle M, Rump LC, Kelm M, Trapp R, Aker S. Peritoneal dialysis relieves clinical symptoms and is well tolerated in patients with refractory heart failure and chronic kidney disease. *Eur J Heart Fail* 2012; **14**: 530-539 [PMID: 22447950 DOI: 10.1093/eurjhf/hfs035]

12 **Bertoli SV**, Musetti C, Ciurlino D, Basile C, Galli E, Gambaro G, Iadarola G, Guastoni C, Carlini A, Fasciolo F, Borzumati M, Gallieni M, Stefania F. Peritoneal ultrafiltration in refractory heart failure: a cohort study. *Perit Dial Int* 2014; **34**: 64-70 [PMID: 24179103 DOI: 10.3747/pdi.2012.00290]

13 **Ponce D**, Balbi AL, Amerling R. Advances in peritoneal dialysis in acute kidney injury. *Blood Purif* 2012; **34**: 107-116 [PMID: 23095409 DOI: 10.1159/000341648]

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