Peritoneal Dialysis for Chronic Congestive Heart Failure

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Key Words

Peritoneal dialysis · Congestive heart failure · Cardiorenal syndrome · Diuretic-resistance

Abstract

Maladaptive responses between a failing heart and the kidneys ultimately lead to permanent chronic kidney disease, referred to as cardiorenal syndrome type 2. In this narrative review, we discuss the pathophysiological pathways in the progression of cardiorenal failure and review the current evidence on peritoneal dialysis as a treatment strategy in cardiorenal syndrome type 2. A patient with heart failure can present with clinical symptoms related to venous congestion even in the absence of end-stage renal disease. Diuretics remain the cornerstone for the treatment of fluid overload related to heart failure. However, with chronic use, diuretic resistance can supervene. When medical therapy is no longer able to relieve congestive symptoms, ultrafiltration might be needed. Patients with heart failure tolerate well the gentle rate of fluid removal through peritoneal dialysis. Recent publications suggest a positive impact of starting peritoneal dialysis in patients with cardiorenal syndrome type 2 on the hospitalisation rate, functional status and quality of life.

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What Happens to the Kidneys in Heart Failure?

The pathophysiology of heart failure is complex, and there are multiple ways in which the heart and kidneys interact in the setting of myocardial dysfunction. The interplay of the heart and kidneys can be grouped into distinct syndromes, collectively referred to as cardiorenal syndromes [1]. In cardiorenal syndrome type 2, maladaptive responses between the heart and kidneys in the setting of a chronic cardiac disorder ultimately lead to or worsen chronic kidney disease (fig. 1) and end up in renal failure [1]. A low cardiac output has historically been the principal mechanism for chronic heart failure manifestations, referred to as ‘forward failure’. The result of a low cardiac output state, in conjunction with decreased renal blood flow, results in the activation of the renin-angiotensin-aldosterone system (RAAS) and increased sympathetic drive, which ultimately lead to increased sodium and water reabsorption at the level of both the proximal and distal nephron. As per Frank-Starling’s law [2], this maladapted volume expansion is meant to maintain and support cardiac output by increasing the end diastolic volumes. In the setting of persisting RAAS and sympathetic nervous system activation and secondary to the systemic inflammation

Fig. 1. Pathophysiological pathways of kidney injury in the setting of myocardial dysfunction. RAAS = Renin-angiotensin-aldosterone system; H₂O = water; Na = sodium; GFR = glomerular filtration rate.

associated with chronic heart failure [3], renal parenchymal changes may develop, evidenced by the presence of albuminuria and histologic changes consistent with focal and segmental glomerulosclerosis and tubulointerstitial fibrosis, ultimately resulting in a progressive decline in the glomerular filtration rate [4]. The state of systemic congestion, referred to as ‘backward failure’, secondary to the maladapted volume expansion and independent of left ventricular ejection fraction, has recently gained interest as a concurrent important factor in the pathophysiology and disease progression of congestive heart failure, with detrimental effects on organs other than the heart itself, such as the kidneys [5]. Indeed, several retrospective and prospective observational studies show a strong relationship between increased right atrial pressure, central venous pressure or intra-abdominal pressure, and renal dysfunction. Moreover, improvement in systemic congestion induces an improvement in renal function [6–12]. The mechanisms of the adverse effects of systemic congestion on kidney function are not completely understood. Increased renal interstitial pressures and pro-inflammatory cytokines released secondary to endothelial stretch have been suggested as possible mechanisms [5]. In addition, the clinical manifestations of systemic venous congestion, including accumulation of fluid outside the lungs (elevated

jugular venous pressure, pleural effusions, hepatic enlargement, ascites and oedema) are leading reasons for hospital admission in patients suffering from heart failure. Systemic venous congestion is an important treatment target, and the relief or prevention of congestion is often considered treatment success. Hence, controlling systemic congestion is important to improve the clinical status of the patient with heart failure, and it could possibly prevent further end-organ damage, such as progressive kidney disease. Therefore, exploring and defining optimal treatment strategies for systemic congestion in the setting of heart failure constitute an important therapeutic endpoint.

Treatment Strategies to Relieve Systemic Congestion

To relieve systemic congestion, either medical treatment, using high-dose diuretics, or mechanical ultrafiltration strategies can be used. Three randomised controlled trials, UNLOAD, RAPID-CHF and CARRESS-HF, comparing ultrafiltration through haemofiltration to diuretic therapy in acute decompensated heart failure did not reveal consistent results in terms of weight loss and kidney function outcomes [13–15]. In UNLOAD and

RAPID-CHF, two studies that included patients with better baseline kidney function compared to CARRESS-HF, ultrafiltration was associated with a significantly greater fluid removal than diuretic therapy. In the CARRESS-HF trial where a more intensive diuretic regimen was used compared to the first two trials, weight loss was similar in the ultrafiltration and medical management groups. However, patients treated with ultrafiltration therapy had increased serum creatinine, whereas serum creatinine levels did not differ between treatment groups in the UNLOAD and RAPID-CHF trials. Patients treated with ultrafiltration in the CARRESS-HF trial also presented with a higher rate of adverse events, mainly catheter-related complications, kidney failure and bleeding complications. Thus, although ultrafiltration by haemofiltration may be a helpful method to achieve euvolemia in patients with acute decompensated heart failure, the available evidence is not consistently in favour of this therapy. The controversy that exists in the results of these studies might be driven by differences in study population and diuretic treatment strategies. Also, whether ultrafiltration itself or rather the mode of ultrafiltration, haemofiltration, drives the effects on kidney outcomes cannot be distinguished from these data.

Diuretics continues to be a cornerstone in the treatment of congestion. However, after chronic use of diuretics, their effectiveness can diminish; this process is called diuretic resistance. A reduction in diuretic effectiveness after chronic use happens due to the adaptations in the kidney to these drugs. These adaptations to diuretics can be classified as those occurring during diuretic action, those that cause sodium retention in the short term and those that increase sodium retention chronically. During diuretic action, the sodium concentration increases in the segments downstream from the site of diuretic action. Given the increased delivered sodium load in the downstream nephron segments, increased sodium reabsorption occurs at these sites. Second, declining diuretic concentrations in the tubule lead to sodium retention by the kidney tubules until the next dose of diuretic is administered ('short-term post-diuretic sodium retention'). Third, a braking phenomenon is described, reflecting increased sodium retention secondary to chronic adaptation of the kidney, whereby the magnitude of natriuresis declines following each diuretic dose [16]. Therefore, mechanical ultrafiltration might have a role as a maintenance treatment in patients with chronic heart failure and systemic congestion resistant to diuretics. The additional salt excretion achieved by ultrafiltration compared to diuretic treatment theoretically could be advantageous in

the setting of heart failure. In this review, we explore the role of extracorporeal ultrafiltration using peritoneal dialysis in the treatment of chronic congestive heart failure.

Rationale for Ultrafiltration by Peritoneal Dialysis in Congestive Heart Failure

The rationale for using peritoneal dialysis (PD) as a mode of fluid removal, rather than extracorporeal haemofiltration, is multiple. Peritoneal dialysis offers gentle ultrafiltration. While ultrafiltration through haemodialysis is associated with myocardial stunning [17–20], a process of persisting left ventricular dysfunction after repeated transient demand myocardial ischemia, peritoneal dialysis is not [21]. Haemodialysis-induced myocardial stunning is associated with progression to fixed systolic dysfunction [22], that is, progression of heart failure. Hence, the modality of ultrafiltration might be a potentially modifiable factor for the progression of heart failure when treating patients with heart disease and diuretic-resistant volume overload. The minimal impact of peritoneal ultrafiltration on haemodynamics would theoretically result in a lower degree of neurohumoral stimulation secondary to ultrafiltration, compared to haemodialysis. As such, in theory, peritoneal dialysis will more likely not stimulate the maladaptive neurohumoral responses in heart and kidney cross-talk already present in heart failure. Several studies indeed suggest PD, compared to HD, to be associated with a slower decline in residual kidney function, a factor known to be associated with survival [23–25]. Because it is a daily or continuous treatment, peritoneal dialysis also allows for effective continuous solute clearance, including sodium and potassium, allowing better up-titration of pharmacological treatment for heart failure, in particular RAAS blockers. The peritoneal cavity access allows for the draining of ascites in the setting of right-sided heart failure and, although it is speculative, providing a permanent outlet for ascitic fluid might reduce intra-abdominal pressure, which has been demonstrated to improve renal function in congestive heart failure [9]. The risks related to a vascular access needed for haemodialysis are avoided: catheter-related blood stream infections (especially in patients with mechanical heart valves or left ventricular assist device) and potential negative effects on cardiac function in the setting of high access flow with arterio-venous fistulas. Last but not the least, peritoneal dialysis is performed at home. The empowerment of patients with a high disease burden through independent dialysis in their home setting can be an important psychosocial aspect of this treatment modality.

Peritoneal Dialysis Prescription in Heart Failure

In peritoneal dialysis, water and solutes are removed over the peritoneal membrane by dwelling dialysate solutions in the peritoneal cavity. An osmotic gradient between the dialysate solution and the capillary blood drives peritoneal ultrafiltration and convective solute removal, while diffusive forces induce additional solute removal, including the removal of sodium and potassium. Currently, commercially available crystalloid solutions are dextrose or amino acid based. They induce solute-free water transport across intracellular water channels, a process called sodium sieving. Colloid osmosis, induced by the larger molecular weight molecule icodextrin, does not activate the water channels, so that all the ultrafiltration occurs at the intercellular pores, where sodium fluxes with the water. This process allows for more sodium removal compared to an equal volume of ultrafiltration with a dextrose-based solution where about half the water removed is through the water channels and so is solute-free [26]. Depending on the patient's need, a peritoneal dialysis prescription can specifically target fluid removal, solute clearance or both. Indeed, by using more frequent exchanges and hypertonic dialysate solutions, both water and high dose solute clearance can be achieved. A single isotonic icodextrin exchange will help in maintaining the fluid status in volume-overloaded patients but with significant residual kidney function. In the end, both residual kidney function as well as patient preference will influence the peritoneal dialysis prescription. Examples of potential peritoneal dialysis prescriptions for patients with heart failure are shown in table 1.

Peritoneal Dialysis for Congestive Heart Failure: Treatment Goals and Established Outcomes

Patients with diuretic-resistant heart failure have a poor prognosis, with high mortality rates and a poor quality of life [27]. A report from 1949 already commented on the continuous peritoneal irrigation in the treatment of intractable oedema of cardiac origin [28]. In the 1960s, when peritoneal dialysis as a renal replacement therapy modality started to be developed, several reports supported the use of peritoneal dialysis for heart failure [29–32]. In the 1990s and early 2000s, several case series and small cohort studies reported good outcomes for peritoneal dialysis when used for the treatment of refractory congestive heart failure in terms of the hospitalisation rate and duration, functional status and quality of life

Table 1. Examples of PD prescription in heart failure

	Day	Night
Scenario 1: adequate residual kidney function but need for fluid removal		
CAPD	dry 1 × 7.5% or 4.25% 2 × 2.5%	1 × 7.5% or 4.25% dry 1 × 2.5%
APD	dry	2–3 × 2.5%
Scenario 2: inadequate residual kidney function thus need for solute and fluid removal		
CAPD	2–3 × 2.5% 2–3 × 2.5%	1 × 2.5% 1 × 7.5% or 4.25%
APD	7.5% or 4.25%	3 × 2.5%

[33–40]. We discuss the results of more recent publications on larger cohorts of patients treated with peritoneal dialysis for the treatment of refractory congestive heart failure. In this particular population, the functional status of heart failure, symptoms related to volume overload and a high number of hospital admissions have a significant impact on the patient's daily living. Hence, these endpoints need close evaluation besides survival per se.

Outcomes on Survival

Retrospective cohort studies on peritoneal dialysis as a treatment strategy for refractory congestive heart failure revealed a broad range of survival time (24 ± 15 months [41], 16 ± 6 months [42]) with 1-year mortality rates between 15 and 42% [41, 42]. Another retrospective analysis in patients with CRS type 2 treated with PD has previously shown a splay of survival time, with mean survival of 12 ± 10 months and a range between 0.3 and 41 months [43]. A prospective observational study showing median survival of 14 months (1–41 months) confirmed once again the variable survival [44]. This prospective trial evaluating 37 patients started on peritoneal dialysis because of refractory congestive heart failure showed serum sodium >132 mEq/l, serum albumin >3.2 g/dl and a hospitalisation rate of <2 days/month the year before starting the treatment to be prognostic factors for survival. A small prospective study by Cnossen et al. evaluated the outcomes of the different modalities of renal replacement strategy, HD or PD, in patients with known hypervolemic treatment-resistant congestive heart failure complicated by renal impairment (PD: $n = 12$; HD: $n = 11$). No significant differences were observed between HD and PD as to the overall survival, although a higher early mortality was noted for HD [45]. The prospective study by Koch

et al. followed 118 incident PD patients with New York Heart Association (NYHA) class III or IV and chronic kidney disease. They showed, not surprisingly, higher mortality rates for patients suffering from NYHA stage IV heart failure (32% mortality at 6 months) compared to NYHA stage III (25% mortality at 6 months). The overall mortality rates were 23, 29 and 45% at 3, 6 and 12 months [46]. No data were available comparing the survival of patients suffering from refractory congestive heart failure who were treated with peritoneal dialysis to those who refused to participate in the study, that is, for those whom a conservative medical management was continued. Given the study designs of the published work on peritoneal dialysis as a treatment strategy for diuretic-resistant cardiorenal syndrome type 2, it is, at the moment, unknown whether a therapeutic strategy including peritoneal dialysis improves the survival rate for this patient population.

Outcomes on the Functional Status

Retrospective studies showed improved functional NYHA classification for patients with refractory congestive heart failure treated with peritoneal dialysis [41, 47]. The prospective study by Cnossen et al. evaluating the effect of renal replacement therapy, PD or HD, on functional status confirmed a significant improvement in the NYHA class, both at 4 and 8 months after the start of dialysis [45]. However, all three studies are confounded by survival bias: mortality is not taken into account when assessing the functional classification during follow-up. It is self-evident that very sick patients will most likely die earlier hence, falsely improve the overall functional classification results during follow-up. In the prospective study by Núñez et al., however, only 1 out of 25 patients died during the 24 weeks of follow-up. At 6 weeks after the PD start and with the full cohort still being alive, the NYHA functional class decreased significantly from 3 ± 0.3 to 2 ± 0.5 . At 24 weeks, when 1 patient had died, NYHA functional class remained at 2 ± 0.6 [48]. Koch et al. performed a comparison of NYHA class at the start of PD (NYHA class III and IV) and after 6 months, including survival outcomes. Their prospectively collected data showed an improved functional NYHA class 6 months after the start of PD for patients surviving the first six months, whereby a higher mortality was noted for patients starting peritoneal dialysis with a NYHA class IV (32% compared to 25% for NYHA III patients). The majority of survivors improved to a functional class NYHA II, irrespective whether they started in NYHA class III or IV [46]. A consistent improvement in NYHA functional status was also found in the prospective studies by Sánchez

et al. [49] and by Kunin et al. [44]. In the Sánchez study, all 17 patients started on peritoneal dialysis for treatment-resistant congestive heart failure improved the NYHA functional status by at least 1 class within the first three months of PD treatment. Only 3 patients' functional status deteriorated again after a mean of 11 ± 4 months [49]. In the Kunin study, the long-term survivors of patients with cardiorenal syndrome type 2 who were started on peritoneal dialysis for refractory congestive heart failure also showed an improved NYHA functional class, by a median of 1 class [44].

Outcomes on Hospital Admissions

Retrospective studies evaluating the clinical effects of PD in patients with diuretic resistant heart failure showed significant reduction in the number and duration of hospitalisations for cardiovascular causes after initiation of PD [42, 43], and in overall hospitalisation rates [41, 47]. Continuous ambulatory PD (CAPD) was the main PD modality in these studies, all limited by survival bias and the absence of a comparator group treated with an alternative renal replacement modality. In the prospective observational study by Núñez et al., patients were invited to participate in a CAPD program performing 2 to 3 exchanges per day if they suffered from heart failure with a functional classification of NYHA class III or IV, had at least two hospital admissions in the 6 months prior to study entry, and persistent congestion despite optimal loop diuretic treatment. Out of the 25 patients started on CAPD, 24 were still alive at 6 months. Compared to a median of 16 (IQR 11–45) hospitalisation days in the 6 months prior to CAPD start, the median number of hospital days was 0 (IQR 0–5) in the first six months after starting PD, corresponding to an 84% reduction in hospital days [48]. No specific data are available on the impact of the deceased patient's information on the results. Beside, no comparison was made to the patient group fulfilling the selection criteria of this study that refused to have PD. In the study by Kunin et al., long-term survivors had a 55% reduction in hospitalisation and a 73% reduction in congestive heart failure daycare visits [44]. The question remains whether PD itself or an increased multidisciplinary medical follow-up, or both, contributed most to the decreased hospitalisation rate. In the prospective trial by Cnossen et al., the impact of any dialysis, PD or HD, on hospitalisation time was evaluated. Twenty-three patients with primary treatment-resistant congestive heart failure complicated by renal impairment were started on dialysis. In this study cohort, eventually, 11 patients were treated with HD and 12 with PD (nightly

intermittent PD or CAPD). For the overall cohort, the number of hospital admissions and hospitalisation time for cardiovascular causes decreased significantly. However, all-cause hospitalisation did not change in the period after starting dialysis compared to the two years before the renal replacement therapy was started [45]. The high dropout rate (9/23 patients) and mortality (7/23) during study follow-up limits the power of this analysis. Given these low numbers, no separate analysis for PD and HD was reported.

Outcomes on Quality of Life

Three prospective studies included a quality-of-life assessment. Two studies used the Minnesota Living with Heart Failure Questionnaire (MLWHFQ), a survey assessing the impact of the cardiac failure on the patient's life during the past month [45, 48]. A substantial improvement in MLWHFQ was noted at 6 and 24 weeks [48]. Compared to the quality of life that existed before starting dialysis, Cnossen et al. still found an improved quality of life according to MLWHFQ in 63% of patients at 8 months follow-up. However, a comparator group without dialysis treatment was not included. The study by Sánchez et al. used the EQ-5D, a validated standardised instrument for use as a measure of perceived state of health [49]. They found PD to be associated with a higher perceived state of health than conservative therapy at 6 months.

Conditions to Perform Peritoneal Dialysis as a Treatment Strategy in Congestive Heart Failure

Given the possible advantages of peritoneal dialysis for patients suffering from cardiorenal syndrome type 2, a peritoneal dialysis program should implement protocols in order to be able to accommodate this particular patient population. These patients need specific attention as to timely referral, catheter insertion techniques and potential anaesthetic risks, evaluation of the need of urgent-start peritoneal dialysis and dialysis prescription adjusted to residual kidney function and fluid removal needed. An absolute requirement to support patients with cardiorenal syndrome with peritoneal dialysis is a good working predialysis education program collaborating with the heart failure clinic. A close collaboration between nephrologists and cardiologists will enable the identification of patients with refractory congestive heart failure who might benefit with peritoneal dialysis. Peritoneal access protocols should involve procedures for pa-

tients with a high anaesthetic risk, as, for instance, bedside percutaneous PD catheter insertion by the nephrologist or interventional radiologist and/or awake surgery by laparoscopic surgical insertion using N₂O insufflation.

Disadvantages of Peritoneal Dialysis as a Treatment Strategy in Congestive Heart Failure

When starting a patient on peritoneal dialysis, some risks as well as some organisational aspects related to the technique need to be considered.

After the insertion of a PD catheter, its function is not guaranteed. Depending on the insertion procedure (open surgical, laparoscopic technique, percutaneous and immediately exteriorised versus buried) and the experience of the operator, primary failure rates, defined as non-functioning access in the first three months after insertion, vary widely. Even if the peritoneal dialysis catheter works well in the beginning, it might stop working over time due to migration, intraluminal obstruction by fibrin fragments or intra-abdominal entrapment by omentum or intra-abdominal organs. Another unpredictable aspect of PD is the unknown ultrafiltration capacity of a given patient to an osmotic or oncotic stimulus. Indeed, in contrast to a haemodialysis machine where a specific ultrafiltration goal can be programmed, peritoneal dialysis requires close clinical follow-up in order to fine-tune the dialysis prescription to the UF needed. The increased intraperitoneal pressure induced by dwelling intraperitoneal dialysate might cause leaks through the exit site or insertion wounds, or cause or aggravate hernias. The infectious risks associated with peritoneal dialysis are exit-site infection, tunnelitis and peritonitis. Although PD-related peritonitis implies certain morbidity and might impair peritoneal membrane function in the long term, PD-related infections are overall easily treatable. When used as a treatment strategy for refractory congestive heart failure in the modern era, peritoneal dialysis has acceptable safety profiles both for infectious and non-infectious complications [41, 42, 45, 46, 48]. Long-term risks associated with peritoneal dialysis, such as its metabolic effects as well as encapsulating peritoneal sclerosis, should not be used as a barrier against this treatment modality in the indication of cardiorenal syndrome type 2 given the overall limited life expectancy of patients with treatment-refractory congestive heart failure.

In order to establish a patient on PD at home, either the patient or the caregiver has to be taught the tech-

niques of peritoneal dialysis. This educational aspect is routine business in every PD program and should not be overlooked in this particular patient population.

Conclusion

Several recent reports suggest peritoneal dialysis to be a beneficial treatment strategy for fluid status control in patients with refractory congestive heart failure in terms

of hospitalisation rates and duration, functional classification of heart failure and quality of life. However, most studies are limited by relatively small numbers, survival bias, the absence of an appropriate comparator group, and intrinsic limitations of retrospective study design. In order to establish a broader evidence regarding the role of peritoneal dialysis as a treatment strategy for diuretic-resistant congestive heart failure, increasing collaboration between centers and collecting data in a prospective registry will be needed.

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