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Review

Peritoneal dialysis in heart failure: focus on kidney and ventricular dysfunction

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Heart failure is a significant health problem worldwide. Despite all the new therapies available nowadays, many patients will reach advanced stages of the disease. Diuretic resistance, kidney dysfunction, and refractory congestion, all highly prevalent in advanced heart failure, frequently complicate the situation, making it more challenging to manage. Ultrafiltration through hemodialysis or peritoneal dialysis can be alternative options to treat fluid overload. Peritoneal dialysis has gained increased interest in the last decades due to several benefits such as functional class improvement, reduction in hospital admissions, improvement in quality of life, and even a reduction in mortality shown by numerous cohort studies. However, the majority of the studies were observational and with a limited number of patients. In addition, the optimal timing for the initiation of this type of therapy and the subgroup of patients who would benefit the most from it is unknown. Hence, randomized controlled trials in this subject are urgently needed. We aim to review the contemporary evidence of peritoneal dialysis in patients with heart failure and diuretic resistance across the spectrum of ventricular dysfunction and degree of renal dysfunction.

Keywords

Peritoneal dialysis; Heart failure; Diuretic resistance; Fluid overload; Renal dysfunction; Ventricular dysfunction

1. Introduction

Heart failure (HF) has reached the status of a global pandemic and is a significant and growing public health problem worldwide [1]. The absolute number of cases worldwide has almost doubled in the last three decades from 33.5 million in 1990 to 64.3 million in 2017 and will keep rising in the years to come [2]. However, the increase in HF prevalence is not always linked with an increase in incident cases. In low-income regions, the incidence continues to rise, driven by a surge in cardiovascular risk factors, adoption of unhealthy lifestyles, and worse access to optimal medical treatment [3]. In higher-income places such as the UK, the Netherlands, or Sweden, the incidence of HF decreases [4] due to a lower severity and better treatment of acute coronary syndrome [2, 5]. Nonetheless, absolute numbers continue to increase mainly driven by population growth and aging.

Regardless of continuous developments in evidence-based therapies, many patients with HF will eventually progress to advanced stages of the disease. Patients with advanced heart failure comprise an estimated 1% to 10% of the overall HF population, in which therapeutic options usually rely on long-term mechanical circulatory support and heart transplantation [6]. However, only highly selected patients will have access to these options. Since most patients are not suitable for such procedures mainly due to age and comorbidities, guidelines usually refer them to palliative care [7, 8].

Fluid overload constitutes the hallmark of most patients with chronic HF, being a primary reason for hospitalization and contributing to HF progression [9]. Kidney dysfunction and diuretic resistance are often associated with fluid overload, making congestion notoriously challenging to manage and portends an ominous prognosis. At this point, the therapeutic options become scarce and limited [10].

2. Kidney dysfunction and diuretic resistance in HF

The pathogenesis of renal dysfunction associated with HF has two main components.

For many years, the reduced cardiac output and fluid redistribution in HF was thought to be the leading cause of renal dysfunction in HF by decreasing renal perfusion and activating the sympathetic nervous system and renin-angiotensin-aldosterone system, which lead to increased renal water and sodium absorption to preserve renal perfusion and glomerular filtration rate. When sustained long term, these mechanisms induce harmful effects on the heart and the kidney by promoting fibrosis, apoptosis, oxidative stress, and activation of inflammatory mechanisms [11]. However, in recent years it has been proposed that decreased forward pressure might not be the more decisive factor associated with kidney dysfunction. Indeed, the increased backward

pressure along the renal veins caused by fluid overload is now considered the primary driver of kidney dysfunction in this setting. The increased backward pressure reduces the glomerulus's net pressure gradient, leading to a reduction in filtration rate and reduced water and sodium excretion worsening renal congestion [12, 13]. Congestion is the leading cause of adverse outcomes in these patients and has a more significant impact than other risk factors such as kidney dysfunction [14]. A 2012 study evaluating mortality and readmissions one year after an episode of acute HF according to the presence of deterioration in renal function combined with signs of persistent congestion found that patients without congestion had better outcomes independently of presenting or not worsening renal function. In contrast, the mortality risk and readmissions were increased in patients with persistent congestion alone and combined with worsening renal function [15]. Similarly, patients treated with aggressive decongestion during an episode of decompensated HF had a significantly lower 180-day mortality, even when this strategy was associated with deterioration in renal function [16]. Thus, congestion control is associated with better clinical outcomes reducing the rate of hospitalization and preventing worsening of the renal function driven by fluid overload [17, 18].

Loop diuretics are the cornerstone of decongestion therapies, but robust clinical evidence to guide their use is sparse and, to this day, is very much empirical [19]. The diuretic dose should be timely adjusted based on an early and repetitive assessment of the diuretic response to achieve successful decongestion in HF [5].

Since diuretic therapy aims to remove the excess sodium and water, urinary output measurement can be a good indicator of diuretic response [20]. High doses of loop diuretics are safe and positively affect dyspnoea relief, change in weight, and net fluid loss [21]. Failure to decongest despite adequate and escalating doses of diuretics is the most common definition of diuretic resistance, a common condition in patients with HF. In a large cohort of elderly patients with decompensated HF, the prevalence of diuretic resistance was 21%, and its presence was independently associated with increased mortality [22]. Another study involving patients with advanced chronic HF found an even higher prevalence of 35% [23].

Several mechanisms are involved in the development of diuretic resistance. Variations in drug pharmacodynamics and pharmacokinetics that affect drug delivery include changes in absorption, distribution, metabolism, and elimination [24, 25]. Drug-drug interactions, such as the association of non-steroidal anti-inflammatory agents (NSAIDs), are also a significant cause of diuretic resistance, producing inhibition of prostaglandins with the consequent reduction of renal perfusion [26, 27]. Additionally, chronic administration of loop diuretics reduces the reabsorption of sodium in the loop of Henle and leads to a higher amount of sodium delivery to the early distal convoluted tube. This causes cellular hypertrophy on this section and eventually augmented reabsorption of sodium and diminished natriuresis, known as the "braking phenomenon" [28, 29]. All these conditions produce a reduced response to the loop diuretic compared to normal subjects, implying a significant increase in loop diuretic dose is needed to gain a modest rise in diuresis [27, 30].

When elevated doses of loop diuretics are not enough to accomplish adequate decongestion, the recommendation is to apply a sequential nephron blockade strategy, which involves the association of other diuretics with different mechanisms of action such as thiazide or thiazide-like agents, mineralocorticoids receptor antagonists, acetazolamide, and more recently sodium-glucose transporter type 2 (SGLT2) inhibitors. However, this approach has not been assessed in large clinical trials [5].

3. Ultrafiltration as an alternative

Apart from the use of diuretics, the only alternative to get rid of excess water and sodium is ultrafiltration. In the last decades, there has been an increasing interest in ultrafiltration as a complementary treatment to diuretics, particularly in patients with HF who develop diuretic resistance.

Ultrafiltration can be achieved through two methods, using extracorporeal circulation during hemodialysis (HD) or by peritoneal dialysis (PD) [31]. Extracorporeal ultrafiltration requires passing the entire volemia through a semipermeable membrane (hemofilter) and, by means of a pressure gradient, separates water from plasma for elimination. PD uses the peritoneal membrane for the liquid interchange; a fenestrated catheter must be placed in the peritoneal fundus through either a minor surgery or by a percutaneous technique [32, 33]. The catheter is used to introduce a variable quantity of liquid in the abdomen. The administrated fluid attracts liquid from the organism through an osmotic effect. When the abdominal liquid is drained, the amount obtained will be greater than the introduced.

In patients with acutely decompensated HF, extracorporeal ultrafiltration has been compared to pharmacological therapy in randomized studies with conflicting results. In the UNLOAD HF trial, benefits such as greater weight and fluid loss and reduced cardiovascular (CV) events at 90-day follow-up were found. In the CARRESS HF study, a strategy of stepped pharmacologic therapy compared with ultrafiltration could not demonstrate the benefit of ultrafiltration; and showed a similar amount of weight loss with an increased number of serious adverse events including access site bleeding, infection, and worsening of renal function. However, it is essential to remark that the ultrafiltration rate in this trial was fixed and elevated, which did not allow any adjustment to the patients' needs and therefore impeding an adequate vascular refilling [34, 35]. Later, the AVOID HF study tried to solve this issue using an adjustable ultrafiltration rate and showed a trend to a longer time to HF and cardiovascular event at 90-day in the ultrafiltration arm. However, the study was prematurely stopped by the sponsor, which im-

pedes drawing firm conclusions from it [36]. Thus, further investigation is needed to clarify the role of extracorporeal ultrafiltration as an alternative to high-dose diuretic treatment in this setting. In this line, the PRURE HF trial results are pending [6].

The current recommendation is that if the high dose diuretic followed by sequential nephron blockade fails, ultrafiltration should be considered. Once chosen, the filtration rate should be adjusted, preferring low rates over several hours, which HF patients better tolerate [6]. Even though extracorporeal ultrafiltration seems to be effective, its potential benefit has only been tested in acute HF decompensation, and its effect is not explored beyond 90 days. In addition, other issues can make it challenging to carry out, such as the need for vascular access that increases the risk of infection and the intermittency of the treatment [31].

4. The role of peritoneal dialysis

PD has been used as renal replacement therapy for many years. Nowadays is not only offered to patients with end-stage renal disease to provide solute clearance and ultrafiltration but is also used in patients with refractory HF and fluid overload to help optimize volume status. The first reported case of treating a congestive HF patient with PD dates back to 1949 [37], but its use has gained progressive interest over the last two decades. Case reports, case series, and small cohort studies have reported favorable outcomes in different patient settings, from severely reduced to preserved ejection fraction and in various types of cardiomyopathies [10, 37–54]. PD constitutes a home-based therapeutic modality that offers the possibility of continuous and gentle removal of excess water and solutes with minimal hemodynamic impact, allows easing the renal venous and intraabdominal pressure while draining ascites and interstitial edema, and has a high capacity of customization to the patient's clinical requirements and daily life. Other benefits to consider in PD are the removal factors associated with deleterious effects in the myocardium (PNA, TNFα, MDF, IL-1, IL-6, among others). These factors have a molecular weight that ranges from 500 to 30,000 Da, and the peritoneum is permeable to these solutes. Their removal from the blood positively affects the half-life of myocardial cells [55, 56]. Moreover, PD may improve the sensitivity to HF treatment.

Sodium removal and not only water is of paramount importance when achieving decongestion. This is suggested by the results of the EVEREST study where the use of tolvaptan, an arginine vasopressin receptor blocker that produces urinary sodium-free water excretion, failed to reduce all-cause mortality, cardiovascular death, or re-hospitalization for HF despite adequate decongestion [57]. Sodium is known to be the main determinant factor of extracellular volume and has a crucial role in the development of congestion. Therefore, sodium removal is the main focus in patients with congestive HF, particularly when patients have an adequate residual kidney function to eliminate waste products [58]. The use of icodextrin solutions, a glucose polymer that has minimal absorption as opposed to glucose-based solutions, produces a sustained colloid osmotic gradient achieving maximal sodium removal, which is appealing in this group of patients [59]. Depending on the patients' needs, two different PD modalities can be applied: continuous ambulatory peritoneal dialysis (CAPD) versus automated peritoneal dialysis (APD). In addition, variations in the volume, frequency, and type of dialytic fluid can be applied. CAPD produces a higher sodium removal than APD [60]. Furthermore, larger dialysate volumes and supine position contrary to upright position can improve sodium removal by recruiting more peritoneal membrane for exchange [58]. Thanks to this, different amounts of liquid and solutes clearance can be achieved [18, 58]. So far, no controlled study has analyzed which peritoneal ultrafiltration modality is the most effective. In our opinion, the most cost-efficient and comfortable modality for the patient is the performance of a single daily exchange with icodextrin with long stays (more than 10 hours). This exchange is usually enough for the patient to reduce the volume overload.

Among the main benefits reported by PD studies, we can find effective decongestion with the correspondent reduction of body weight, improved functional class, hospital admissions, and days of hospitalization. All these benefits ultimately translate to an improvement in quality of life. Improvement in cardiac function has also been explored and found in some studies [42, 43, 61]. However, it appears that in most studies, there was a lack of correspondence between an improvement in symptoms and a significant improvement in cardiac performance [31]. The decrease of the renal venous and intraabdominal pressures has been associated with restoration of diuretic responsiveness and a slower decline in renal function [12]. In addition, the reduction of days in hospital implies that there could be a beneficial effect on the financial burden of the disease. This was analyzed and confirmed by Sanchez *et al.* [52], who evaluated the costs of treating patients undergoing PD compared to the standard diuretic therapy finding a fourfold reduction in expenses. However, the authors remark that this should be further analyzed in more extensive trials.

In patients with refractory HF treated with conventional therapies, mortality rates are as high as 50% at six months and 75% at one year [62]. Regarding the potential positive effect on survival, the survival rates at one year among different cohorts highly differ. A review that analyzed the data from 8 different cohorts found that the 12-month survival rate varied between 47 and 95 %. This observation is mainly attributed to the lack of clarity and uniformity of the selection criteria used by the various studies and due to the variability in the therapy, both in terms of dosage and associations [31]. Nuñez *et al.* [54] who found a lower rate of death/readmission of patients treated with PD compared with standard diuretic medical therapy at 1-year follow-up. Furthermore, several studies that compared the mortality of their population with the expected mortality at one year ac-

cording to the Charlson comorbidity index showed that the rate of deaths was considerably lower, insinuating a substantial survival benefit [39, 45, 47, 51, 52, 61]. However, due to the type of studies carried so far that generally are not randomized, not controlled, and with a limited number of patients, firm conclusions cannot be extracted. Table 1 (Ref. [38, 41–43, 45, 46, 51–55, 63]) summarizes a selection of the main PD cohort studies with baseline patient characteristics and main study findings.

Despite all the potential benefits of PD, not all patients can undergo this treatment modality. Clinical contraindications for PD include abdominal inflammatory processes such as Crohn's disease, ulcerative colitis, current Clostridium difficile infection, and end-stage liver disease with ascites. The main anatomic limitation to DP is unrepaired hernias, as PD could increase their size, and the presence of ostomies or feeding tubes is a relative anatomic contraindication [64]. Furthermore, anesthetic risks may contraindicate the insertion of the PD catheter. In addition, after the catheter is placed, the ultrafiltration capacity of a given patient is unpredictable, requiring a close clinical follow-up to find the optimal ultrafiltration rate prescription [65]. Finally, the patient or caregiver must be able to perform the exchanges, and an excellent predialysis education program directed is critical.

As with most medical interventions, complications can appear. Fortunately, the incidence of such events in PD is low. Mechanical complications include leaks through the exit site or insertion wounds, hernias, and catheter dysfunction. Infectious complications include exit-site infection and peritonitis, and, in general, these are easily treatable [45, 65]. A systematic review of 14 PD studies in HF from 2015 by Lu *et al.* [66] reported that the mean incidence of peritonitis was 14.5% per year (ranging from 1.6 to 37.7%). This incidence was not higher than the rates in standard chronic PD patients with end-stage renal disease (ESRD), in whom peritonitis rates have been reported to be as high as 51.1%. Mechanical complications were seldom reported, and thus, a specific analysis could not be performed.

To date, it is still not clear which patients with HF and refractory congestion benefit the most from PD. To elucidate this, several authors have tried to find prognostic markers related to higher mortality and longer survival after the initiation of PD therapy. Age, diabetes mellitus [38, 53], higher brain natriuretic peptide (BNP), and serum urea [38] have been significantly associated with death. In contrast, higher serum albumin, serum sodium, and lower hospitalization rate before starting PD seem to be prognostic factors for long-term survival [41].

Whereas most studies on PD are observational, some attempts have been made to carry out randomized controlled trials. The first attempt at a multicentre randomized controlled trial was recently made in the UK; the trial aimed to recruit 130 patients with chronic HF and diuretic resistance on optimal medical therapy in 6 centers. The participants were randomized to continuation of standard medical treatment vs. standard medical treatment plus PD. Outcomes included change in the 6-minute walk test, quality of life, hospitalizations, and mortality. After two years, the trial had to stop due to inadequate recruitment; out of 290 screened patients, only 20 met the inclusion criteria, and 10 were recruited. Barriers to recruitment included frailty, unwillingness to engage in invasive therapy, and suboptimal coordination between cardiology and nephrology services. The difficulty in recruiting patients highlights the potential limitations to using this therapy on a daily basis [67].

Nowadays, PD should be considered in patients in New York Heart Association (NYHA) functional class III to IV, with repeated episodes of volume overload (hospital admissions or need of intravenous diuretics) and optimized medical and device treatment with no contraindications for PD.

5. Degree of renal dysfunction and PD

As described before, patients with HF commonly present with various degrees of renal dysfunction [68]. According to a meta-analysis from 2006, approximately 50% of patients with chronic HF present with impaired renal function [69]. Moreover, in another report, a prospective cohort of 754 outpatients with congestive HF showed that 16% of patients had creatinine clearances of $<$30 mL/min and 39% between 30 and 59 mL/min [70]. PD has been used successfully in HF patients with refractory fluid overload with and without ESRD.

5.1 Non-ESRD and PD

For those patients with HF and kidney dysfunction that is not severe enough to require dialysis as a renal replacement (stages IV and above), the studies have, in general, reported positive outcomes [17]. The mean estimated glomerular filtration rate (eGFR) highly differs among the different cohorts going from 14.6 mL/min to 35 mL/min. However, most of these studies did not find a relationship between survival and the degree of kidney dysfunction [44, 53]. Courivad *et al.* [42], with one of the largest PD cohorts, aimed to analyze this specific aspect dividing their patients into three categories based on eGFR, higher than 30 mL/min, 20 to 30 mL/min, and 15 to 30 mL/min. Patients with worse renal function were significantly older and less frequently treated with aldosterone receptor antagonists, though these conditions did not influence the survival rates of patients. Two studies have found a relationship between renal dysfunction at baseline and positive outcomes, yet with conflicting results. In the study by Pavo *et al.* [63], patients with treatment success predefined as survival of at least 12 months combined with improved quality of life, a decline in hospitalization days, or both had better kidney function determined by 24-h-GFR and higher urinary volume. However, an association with eGFR was not found. On the other hand, Kunin *et al.* [41] found that in their study, patients in the lower survival quartile (less than three months) had a higher eGFR. The reason for this observation is not apparent.

In terms of the progression of kidney dysfunction after starting the PD treatment, a 2015 meta-analysis of 6 studies

Table 1. Summary of studies of peritoneal dialysis in heart failure.

Author (year)	Study design	Number of patients	Age	eGFR	LVEF	NYHA class	Charlson comorbidity index	1 year survival	Mean survival	Improved functional class	Improved QoL	Reduced hospitalization	Improvement in ventricular function	Comment
Gotloib (2005) [51]	Single center, prospective, non-randomized	20	65.7 ± 7.6	14.84 ± 3.8 mL/min (MDRD)	31.2 ± 4%	IV	7.8 ± 1.8.	90%	n.a.	*	n.a.	n.a.	*	Significant improvement of left cardiac work index, reduction of the systolic times ratio, lower thoracic fluid contents
Sanchez (2010) [52]	Single center, prospective, non-randomized	17	64 ± 9	35 mL/min ± 6 (21–62)	33 ± 3%	7 III–10 IV	6.9 ± 1.7	82%	n.a.	*	n.a.	*	n.a.	Cost effective, no effect on LVEF
Cnossen (2010) [53]	Single center, retrospective study	24	67 ± 10	14.8 ± 12.1 mL/min (MDRD)	33 ± 16%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	*	n.a.	Age and diabetes seem to be significant prognostic factors, but not LVEF
Nuñez (2012) (EJH) [54]	Single center, prospective, non-randomized	25	75.1 ± 8.2	33 mL/min (21–42). MDRD	40 ± 14%	III–IV	5 ± 2	n.a.	n.a.	*	*	n.a.	n.a.	Improvement in biochemical profile
Cnossen (2012) [55]	Single center, prospective, non-randomized	23	66 ± 21	14.6 ± 12.1 mL/min	37 ± 20%	4 III–19 IV	4.9 ± 1.2	n.a.	16 months	*	*	*	n.a.	Hospitalization for cardiovascular causes, but not for all causes, was reduced
Koch (2012) [38]	Single center, prospective, non-randomized	118	73.2 ± 11.4	19.2 ± 13.3 mL/min	43.5% (30.0–55.5)	49.2% III–50.8% IV	n.a.	55%	1.7 years	n.a.	n.a.	n.a.	n.a.	Age, DM, BNP, and log serum urea remained significantly associated with death
Kunin (2013) [41]	Single center, prospective, non-randomized	38	66.5	33.6 ± 17.6 mL/min	28 ± 16%	IIIb–IV	n.a.	58%	14 months	*	n.a.	*	n.a.	Decreased dependence on intravenous diuretics and vasoactive medications
Bertoli (2014) [43]	Multicenter, retrospective study	48	74 ± 9	21 ± 10.3 mL/min	30 ± 11%	46% IV 48% III 6% II	n.a.	85%	n.a.	*	n.a.	*	*	Increases in hemoglobin, and reductions PAPs, and diuretic dosage
Courivad (2014) [42]	Multicenter, retrospective study	126	72 ± 11	33.5 ± 15.1 mL/min	38 ± 19%	n.a.	n.a.	n.a.	16 months	n.a.	n.a.	*	*	Significant improvement in LVEF
Pavo (2018) [63]	Single center, prospective, non-randomized	40	65 (IQR 59–70)	19.4 (10–34) MDRD	29% (23–36)	n.a.	n.a.	55%	n.a.	n.a.	*	*	n.a.	Focused on the predominance of backward failure
Grossekettler (2019) [46]	Multicenter, prospective, non-randomized	159	72.8 ± 12.1	24 ± 11.3 mL/min	31 ± 13%	II–IV	n.a.	61%	n.a.	*	n.a.	*	n.a.	PD significantly reduced both number and days of hospitalization for all causes also in patients with declining EF
Wojtaszek (2019) [45]	Single center, prospective, non-randomized	15	72 ± 9	32.0 ± 11.0	34.3 ± 12.4%	III–IV	9 ± 1.2	93%	n.a.	*	n.a.	*	*	More than 80% decrease in hospitalization rates, observed already after the 1st months of the treatment

n.a., not analysed/available; QoL, Quality of life; eGFR, estimated glomerular filtration rate.

involving 282 patients with chronic kidney disease stage IV and above evaluated the difference in eGFR pre- and post-PD. eGFR was not statistically different after PD treatment verifying that this intervention can preserve renal function. Interestingly, the authors propose that this may be a critical factor in the improvement of survival and cardiovascular outcomes [66].

5.2 ESRD and PD

In patients with end-stage renal dysfunction, fluid removal can be performed either by hemodialysis (HD) or PD. Whether one or the other is the best option for renal replacement in patients with concomitant HF is still a matter of debate. Several theoretical advantages in favor of PD have been suggested. Myocardial stunning is present in patients undergoing HD even in the absence of significant coronary artery disease [71]. This can potentially lead to a reduction in ventricular systolic function long term, increasing the risk of HF [72]. PD is not associated with this phenomenon [73]. PD has a potassium lowering effect which reduces the risk of hyperkalemia, and it has been reported that up to 60% of patients with ESRD tend to hypokalemia in this setting [74]. This could be advantageous since patients would be able to reach target doses of potassium-sparing drugs such as mineralocorticoids receptor antagonists and renin-angiotensin-aldosterone system inhibitors, improving the prognosis of HF [18]. Other risks related to HD, such as the need for anticoagulation of extracorporeal circuit, intravascular infections or thrombosis, and the adverse hemodynamic effects in the form of overload associated with an arteriovenous fistula, can also be avoided with PD [18, 31]. Furthermore, a lower probability of neurohormonal activation provided by the slow removal of water and solutes has also been described in PD [65]. Finally, as already mentioned, various studies suggest better preservation of residual renal function associated with PD compared to HD [75, 76].

Regardless of the proposed advantages of PD, studies in this group of patients report conflicting results suggesting that the potential benefits might not translate into better clinical outcomes. In a cohort of 139 patients with ischemic cardiomyopathy and end-stage kidney disease, which initiated PD versus HD, there was no difference in 2-year mortality and cardiac hospitalization [77]. Furthermore, based on an extensive registry from the United States, Stack *et al.* [78] reported a higher mortality risk among ESRD patients with HF treated with PD compared with those treated with HD. However, it must be pointed out that patients in this study were included between 1991 and 1997 when newer dialysate solutions and technologies were still not available [42]. However, in a more recent report from a French registry of patients recruited between 2002 and 2008, survival was compared according to dialysis modality (933 on PD and 3468 patients on HD). Once again, significantly higher mortality risk was associated with PD [79]. Moreover, based on a national registry from Taiwan involving more than 35,000 patients, Wang *et al.* [80] compared the survival of ESRD patients with HF and found a significantly inferior survival rate in patients receiving PD treatment compared to HD. Suboptimal management of congestion has been proposed as a possible explanation for these results, as it seems that initiation of PD in patients with ESRD does not achieve a marked improvement in fluid overload, which remained a prevalent problem in a subgroup of PD patients [17]. This is suggested by a multicentre study of patients using PD in which only 40% were found to be euvolemic [81].

Interestingly, when analysing patients with incident ESRD starting dialysis who do not present yet with cardiovascular disease, the situation is different. An Italian registry with more than 4000 patients recruited in Lombardy between 1994 and 1997 reports that the risk of de novo cardiovascular disease, including HF and coronary artery disease, was not statistically different with HD vs. PD [82]. In addition, a more recent report from Taiwan that included patients with newly diagnosed with ESRD from 2000 to 2010 showed no difference in de novo ischemic heart disease. Still, HD was indeed significantly associated with a higher risk of de novo HF. However, this excess risk under HD treatment quickly disappeared after the first year [83, 84].

6. Ventricular function and PD

The ventricular function has been evaluated in almost all cohorts using left ventricular ejection fraction (LVEF). Patients with HF across the whole spectrum of LVEF have been treated with PD. Most studies that looked into prognostic markers could not find a correlation between LVEF and survival after starting PD [38, 41, 53]. Nonetheless, a couple of studies suggest that there might be a bigger benefit related to ejection fraction subgroups. Courivad *et al.* [42] categorized their patients into three groups according to LVEF, preserved (defined as LVEF >45%), moderately reduced (LVEF 30 to 45%), and severe dysfunction (LVEF <30%). A trend towards worse survival in patients with severe dysfunction and preserved ejection fraction compared with the moderately reduced group was observed, particularly during the first year after therapy initiation. Furthermore, patients who remained alive beyond the mean survival time of the cohort (16 months) had a significant improvement in LVEF during the first year. On the contrary, patients who died prematurely had a stable ventricular function throughout follow-up. In a similar study, the group of Grossekettler *et al.* [61] made a comparison between patients with preserved (>40%) versus reduced ejection fraction (<40%). Their findings were that even when both groups improved the NYHA functional class, the benefit in total number and days of hospitalization for all-cause was only seen in the patients with preserved ejection fraction. The authors propose that as pulmonary hypertension and renal dysfunction are slightly higher in patients with preserved ejection fraction, the burden of cardiorenal interaction would be more substantial in this group.

Improvement in LVEF after initiation of PD has been reported by several authors [42, 51, 61, 85], while others failed

to find a significant change [43]. However, it is essential to remark that the studies with the largest populations so far were able to report such an improvement [42, 61]. Moreover, a meta-analysis involving thirteen studies with a total of 537 patients examined the difference of LVEF before and after PD finding a significant improvement of 4.08% [66]. Although the reason for this finding remains elusive, beneficial hemodynamic effects related to fluid extraction moving the Frank-Starling curve to the left [18] and removal of inflammatory mediators such as interleukin-1, tumor necrosis factor-alpha, and interleukin-6 have been proposed as potential explanations for this [55, 56].

Right ventricular dysfunction combined with fluid redistribution is considered the last sequela of patients with advanced HF. Only one PD study has focused on patients with right ventricular failure with and without left ventricular dysfunction. In this particular study, patients with extended ascites, higher systolic pulmonary artery pressure, more marked impairment of right ventricular function and tricuspid valve insufficiency, higher residual renal function, and those who could perform PD without assistance benefited most from this therapy [63].

7. Conclusions

PD stands as a valuable and accessible option for treating advanced HF patients with refractory congestion; multiple benefits have been proposed to this therapeutic option. Important outcomes such as a decrease in hospitalization, improvement in functional class, quality of life, and even a potential benefit in survival seem to be consistent findings in most studies. However, as most of the studies are limited to observational cohorts, the results might be biased and can only hint at hypotheses. Hence, larger randomized controlled trials in this setting are of utmost importance and urgently needed. Finally, PD is often offered as a last resort therapy to severely ill patients. Considering this option at an earlier stage of the disease in a more proactive approach could be helpful. However, further well-designed studies are needed to confirm the potential positive outcomes of PD treatment and to identify patients who would benefit the most from this intervention and those in which the treatment with PD could be futile.

Author contributions

NF conceived the review. ROM, FB and NF contributed to the content of this article and made substantial contributions to the manuscript. ROM, FB and NF read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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