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Review

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Kidney Replacement Therapy in Cardiorenal Syndromes

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Abstract

Cardiorenal syndromes (CRS) have increasingly been recognized as distinct disorders that affect the heart and kidneys simultaneously, either with acute or chronic onset. The different types share common pathophysiological characteristics. The concept "cardiorenal" shall emphasize the inter- or even multidisciplinary approach to respective patients. Anticongestive therapy becomes mandatory in many subjects that suffer from CRS. In recent years, the role of dialysis treatment in a broader sense has been investigated in CRS in more detail. We performed a search for studies related to the topic in the following databases: MEDLINE, PROSPERO, and Web of Science. The following keywords were used for reference identification: "CRS", "cardiorenal syndrome", "dialysis", "hemodialysis", "hemofiltration", "renal replacement therapy", "kidney replacement therapy", "peritoneal dialysis", and "aquapheresis". Finally, a total number of 22 studies, partly performed as retrospective cohort studies, and partly designed as prospective investigations, were included. The selected studies evaluated different modes of peritoneal dialysis (PD) or of non-PD procedures including intermittent hemodialysis, continuous procedures, and so-called aquapheresis. Inclusion and outcome parameters were almost not comparable between selected trials. Some studies revealed dialysis as effective, with reasonable tolerability. Particularly so-called "pure" ultrafiltration (e.g., aquapheresis) was associated with higher rates of adverse events. Future studies should be designed in a more homogenous manner, particularly concerning the inclusion criteria, the respective dialysis procedure applied, and endpoints in the short- and long-term.

Keywords: Kidney replacement therapy; Cardiorenal syndrome; Ultrafiltration; Refractory hypervolemia; Peritoneal dialysis

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Introduction

Cardiorenal syndromes (CRS) are disorders with common pathophysiological characteristics [1]. The first description of that was published in 1913 (A clinical lecture on paroxysmal dyspnea in cardiorenal patients: with special reference to "cardiac" and "uremic" asthma: delivered at University College Hospital, London, on November 12, 1913) [2]. Today, the concept "cardiorenal" highlights the inter-/multidisciplinary character of the diseases, not only from a pathophysiological but also a therapeutic perspective. For a long time, five distinct CRS types have been differentiated. In all of these, heart and kidney functions are variably impaired at the same time, either with acute or chronic onset. In 2013, Hatamizadeh and colleagues [3] emphasized the fact that in clinical practice, it is more or less impossible to identify which process or organ was initially responsible for cardiorenal dysfunction. Thus, the initial concept may not be suitable for improving the clinical management of CRS in many cases.

From the nephrologist's perspective, dialysis usually becomes mandatory, if either systemic toxification or hypervolemia due to kidney excretory dysfunction can no longer be controlled with pharmacological measures. In CRS, however, dialysis in a broader sense (extracorporal hemo- or ultrafiltration, conventional hemodialysis, continuous procedures, and peritoneal dialysis (PD)) may be initiated even if kidney function is impaired only moderately. The most important reason is refractory (diuretics-resistant) hypervolemia. In recent years, several non-pharmacological treatment regimens have been investigated. Among those were PD, conventional hemodialysis, and so-called aquapheresis. The current article intends to briefly summarize studies on dialysis therapy in CRS. It needs to be mentioned that the current literature is quite heterogenous: 1) many trials were initiated before the concept of CRS arose "officially"; 2) treatment groups are almost not comparable between studies (refractory heart failure without the diagnosis of CRS [4], CRS type 1 only [5], CRS types 2 and 4 [6]); 3) control groups were often missing; 4) outcome parameters differed significantly between several investigations. Therefore, a meta-analysis is momentarily difficult to provide in our opinion.

Firstly, we will summarize the most important pathophysiological characteristics of each classical type of CRS [1]. Then, the data on PD and non-PD will be discussed. One paragraph is dedicated to kidney replacement therapy (KRT) in CRS type 5 since this type includes heart and kidney dysfunction in sepsis. Finally, we will outline which particular aspects related to dialysis in CRS must be addressed in future investigations.

Pathophysiology

CRS type 1: acute heart failure induces acute kidney injury (AKI)

Acute heart failure can induce AKI through the following mechanisms: low cardiac output syndrome, venous congestion, and the activation of humoral responses [7]. Additional factors that potentially aggravate kidney dysfunction are either exogenous in nature (e.g., contrast media, diuretics) and/or the result of heart failure-associated immune activation [7]. Among the humoral responses are stimulation of the renin-angiotensin-aldosterone (RAA) and sympathetic nervous system activation. Particularly the former induces volume retention, further aggravated by reduced glomerular filtration of solutes and water in established AKI. AKI significantly worsens the prognosis of heart failure subjects: it has been identified as an independent risk factor for lower 1-year survival [8].

CRS type 2: chronic heart failure accelerates chronic kidney disease (CKD) progression

The 2012 published KDIGO guidelines [9] provide definition criteria of CKD. The management of CKD requires the control of so-called progression factors, circumstances that accelerate the loss of kidney function in the long term. Low cardiac output in chronic heart failure may be regarded as an important mechanism responsible for accelerated CKD progression [1], although venous congestion is presumably involved also [1]. Lower blood flow to the kidney and other organs does not only reduce tissue perfusion but also result in microcirculatory endothelial cell dysfunction (ED). ED on the other hand is an established risk factor for atherosclerosis [10]. Although chronic heart failure is currently not understood as a CKD progression factor, it most likely should be added to the list of progression factors.

CRS type 3: AKI induces acute cardiac dysfunction

AKI affects increasing numbers of patients treated in hospitals in central Europe and the US. It is estimated that AKI establishes in up to 20% of all in-hospital patients [11]. The diagnostic criteria have been updated for the last time in 2012 [12]. Early AKI diagnosis remains difficult, although some progress has been achieved with the identification of new biomarkers [13]. The term "acute cardiac dysfunction" must be used in a broader sense. It encompasses acute failure with low cardiac output, acute ischemia with or without ventricular failure, and arrhythmias [1]. The most important mechanisms include water and solute retention with subsequent volume expansion, electrolyte and acid-base disorders such as hyperkalemia and acidosis, and RAA and sympathetic nervous system activation. Finally, AKI is an inflammatory disease, no matter what type of disease/condition was the primary cause [14, 15]. Kidney inflammation in AKI modulates the systemic inflammatory response, including monocyte and endothelial cell activation [16]. Such events increase the risk for acute cardiac dysfunction also.

CRS type 4: CKD aggravates chronic heart failure

The prognosis of CKD patients critically depends on cardiovascular morbidity [17]. Many CKD patients will never require dialysis since they simply will not survive long enough. The most important factors responsible for chronic heart failure in CKD are chronic retention of water and sodium with subsequent hypertension, the uremic milieu *per se*, and anemia due to reduced synthesis of erythropoietin [18]. Particularly anemia has been identified as a major problem in CRS. The triad of heart failure, CKD, and anemia has been defined as cardiorenal anemia syndrome (CRAS) [19]. Erythropoiesis-stimulating agents are established therapeutics for treating renal anemia *per se* but are not in use for anemia control in heart failure so far. However, prolyl-hydroxylase inhibition, as for instance mediated by the substance Daprodustat [20], may become an option in CRAS since it potentially promotes cardiac repair independently from both, the erythropoiesis and the iron metabolism [21]. Another problem is the accumulation of phosphate and the increased production of fibroblast growth factor-23 [22]. The latter has been identified as a potent inducer of left ventricular hypertrophy [23]. High serum phosphate and calcium levels perpetuate vascular and extravascular calcifications.

CRS type 5: heart and kidneys are affected by a systemic condition

The fifth type of CRS encompasses a heterogeneous group of diseases that potentially affect the heart and kidneys. Among those are sepsis, autoimmune disorders such as systemic lupus erythematosus and granulomatosis with polyangiitis, amyloidosis, and diabetes mellitus. There are no common mechanisms by which the heart and kidneys are affected since such diseases are too heterogeneous in terms of etiology and pathogenesis. We therefore will omit a more detailed discussion.

As described earlier, the general concept of CRS and its respective types has changed over the last decade, since clinically, the exact identification of a certain type may become challenging or even impossible during follow-up [3]. Common hallmarks of all CRS are impaired excretory kidney function, cardiac dysfunction, hemodynamic abnormalities, aggravated inflammation, and other processes. These require an integrated therapeutic approach, no matter what type of pathology may have emerged at the beginning.

KRT in CRS: General Considerations

The different KRT procedures differ in one or more of the following qualities: duration of individual treatment sessions, the processes which predominantly mediate removal of solutes

and water (dialysis vs. hemodiafiltration), and the (net effluent) flow if hemo(dia)filtration is considered. The term "intermittent" usually describes dialysis sessions performed every day or every other day, with 4 - 5 (- 6) h of treatment time per session. The blood flow rate often ranges from 200 to 400 mL/min, and dialysis solution is delivered at a rate of 500 mL/min. Slow extended daily dialysis (SLEDD; alternative: sustained low-efficiency daily dialysis [24]) is usually performed daily, and treatment sessions take between 6 and 12 h, respectively. The blood and dialysis flow rates are adapted to 100 - 150 and 100 - 300 mL/min. Continuous procedures, either performed as hemodialysis or hemodiafiltration, may last as long as 24 h per day. The blood flow rate is typically adjusted to 100 - 150 mL/min, and dialysate solution flows at 20 - 100 mL/min. It needs however to be mentioned, that both, the blood and the dialysate flow rates can vary significantly, depending on disease-associated factors and preferences of the nephrologist in charge. If continuous dialysis is combined with hemofiltration, either in pre- or post-dilution mode, the effluent flow varies between 20 and 35 mL/kg/h with a net ultrafiltration rate of about 13 mL/kg/h. In the clinical context, continuous procedures are generally believed to affect hemodynamic stability less. Therefore, continuous procedures are often favored in hemodynamically unstable subjects. However, studies published so far failed to prove significantly different mortality rates between continuous KRT and other procedures employed to treat AKI subjects in the intensive care unit (ICU) [25-27]. SLEDD may be performed at lower costs and is less time-consuming.

From the nephrologist's point of view, KRT becomes mandatory if kidney excretory function deteriorates in a way that systemic consequences are no longer controllable with pharmacological measures. Common reasons for initiation of dialysis are refractory hyperkalemia, acidosis, hypervolemia, and symptoms that indicate systemic toxification (uremia) [9]. In patients with CRS, KRT may become necessary even if kidney excretory is not critically impaired. Many subjects with simultaneous heart and kidney failure (acute or chronic) develop refractory hypervolemia [28] without symptoms of systemic toxification. In this context, whole-body sodium overload plays a critical role in the induction of hypervolemia and congestion. In heart failure, sodium elimination is impaired in the early or subclinical stages of the disease [29] and sodium determines the extracellular fluid volume. The elimination of sodium is therefore the primary aim of any decompensation therapy [30].

PD

As summarized by Kazory and Bargman [31], PD is potentially beneficial in subjects with impaired cardiac function. The most important advantages are the possibility to eliminate fluid in a continuous manner, with minimal impact on hemodynamics. In addition, sodium elimination may be adapted to the respective needs of the patient and, finally, PD allows preserving remnant kidney function longer than extracorporal therapy. Studies on PD in acute situations such as acute heart failure or AKI are missing since, in most facilities, the technical requirements are not available.

The feasibility of PD in heart failure patients has been studied since the 1960s. As discussed in a recent review [31], early studies had significant limitations, particularly since patient numbers were usually low. In these early studies, and in several newer investigations, the term CRS was not used at all, simply because the concept of cardiorenal diseases arose by the end of the first decade of the new millennium [1]. Nevertheless, we will include some of these studies since they offer information about the tolerability of PD in heart failure in general. The articles will be discussed in chronological order from older to more recent trials.

The first study that needs attention was published in 1968 [32]. PD was performed in 16 subjects with refractory heart failure. Twelve patients achieved remission with an average weight loss of 6 kg. While the general tolerability was well, the authors reported that excessive volume depletion in some cases could have contributed to hypotension and death.

In 1970, Chopra and colleagues [33] published a case study series about four patients with refractory pulmonary edema due to myocardial infarction. In three subjects, PD substantially reversed fluid overload.

A 1985 published article by McKinnie et al [34] reported the long-term use of PD in one individual with refractory heart failure. The article showed PD as a therapeutic option that may be applied for 2 years or even longer. Comparable observations were published 1 year later [35], and eight instead of one patient were included. In 1996 finally, Tormey et al [36] reported about three individuals with refractory heart failure that were treated with intermittent ambulatory PD for 18 ± 10 months. The procedure reduced the overall in-hospital time and improved the subjects from stage IV to II according to the New York Heart Association (NYHA).

Lager studies were published more than 10 years later. Koch et al [37] prospectively included 118 individuals with chronic heart failure (49.2% NYHA stage 3, 50.8% NYHA stage 4). All subjects suffered from CKD with a mean overall serum creatinine of 3.70 (2.50 - 5.41) mg/dL. PD was initiated due to the refractory nature of the heart disease, defined as persistent hypervolemia despite the use of RAAS inhibitors and/or loop diuretics and/or thiazides and/or betablockers and/or aldosterone antagonists. The term "and/or" is intended to indicate that not all of the different types of drugs were simultaneously applied to all individuals. PD was performed as nocturnal dialysis, 12 h per night, respectively. The mean follow-up was about 1 year. A control group was not included. At 3, 6, and 12 months, overall survival rates were 77%, 71%, and 55% (95% confidence interval (CI): 45 - 64). Age, diabetes mellitus, serum urea, and brain natriuretic peptide were associated with mortality in a significant manner.

Another study published in the same year [38] was designed in a retrospective although multicentric manner. A control group was also missing. A total number of 48 subjects were included, and all of these patients suffered from severe and refractory heart failure despite maximized drug therapy. The respective PD regimens were quite different, and 10 Italian nephrology departments participated. The most important finding was a reduction in the duration of hospitalization due to heart insufficiency.

In 2012, Courivaud et al [39] published outcomes of all refractory heart failure patients (n = 126) that received PD between January 1995 and December 2020 (two French medical centers). The procedure significantly reduced the number of days of hospitalization for acute heart failure and improved left ventricular function.

In a 2017 published prospective trial, Ponce and colleagues [5] included subjects with CRS type 1, and a control group was not defined. A total number of 64 subjects were included, and all of these received high-volume PD with a prescribed Kt/V per session of 0.5. It became apparent that non-survivors were older, suffered from acute coronary syndrome (ACS) more often, and showed a more positive fluid balance after the second PD treatment session, respectively.

Pavo et al [4] performed a prospective cohort study on subjects with refractory right heart failure (± left heart insufficiency). The following definition was used to recruit patients: persistent right heart congestion under intensified treatment with diuretics and/or two or more hospitalizations within 6 months due to cardiac decompensation and/or AKI due to drug-based therapy of cardiac decompensation. It needs to be emphasized that the design did not exclusively consider CRS. Survival rates through years 1 to 3 were 55%, 35%, and 27.5%. The number of hospitalizations due to cardiac decompensation declined and several qualities were associated with the higher benefit of PD: extended ascites, better residual renal function, and no help needed in performing PD.

In 2018, Shao et al [40] published a prospective study with 36 subjects included. Two groups were defined as CRS type 2 (A) and CRS other types (B), and patients underwent PD with a follow-up until death or PD discontinuation. Multivariate regression analysis showed CRS type 2 as an independent risk factor for death on PD; in addition, left ventricular ejection fraction (LVEF) improvement was limited to group B.

Xue and colleagues [6] published a retrospective cohort study in PD patients with various degrees of heart failure (non-CRS, acute heart failure, CRS types 2 and 4). The observational period lasted from 2006 to 2016, and a total of 748 subjects were included (distribution: 466 (62.3%) non-CRS, 214 (28.6%) acute heart failure, 27 (3.6%) CRS type 2, and 41 (5.5%) CRS type 4). The respective cardiovascular survival rates were 93%, 92%, 84%, and 81% by the end of year 1, and 67%, 59%, 55%, and 54% by the end of year 5. However, after adjusting for confounding factors, CRS types 2 and 4 were not independently associated with increased all-cause mortality, while CRS type 4 alone was. Thus, higher all-cause and cardiovascular mortality observed in CRS was attributed to higher age and higher cumulative morbidity, rather than to CRS *per se*. Type 4 CRS was suggested to represent a particular problem that needs to be addressed separately.

Another retrospective, data-based cohort study, in which the authors extracted data from the registry of the German Society of Nephrology, was published in 2019 [41]. They evaluated patients included between January 2010 and December 2014, with a total number of 159, and all subjects suffered from refractory heart failure. Nevertheless, the diagnosis CRS was not made distinctively. They found both improvement of the NYHA stage and of hospitalization due to decompensation.

Wojtaszek et al [42] performed a single-center pilot study in refractory heart failure. The refractory nature of the disease was defined as resistance to so-called updated therapy in conjunction with at least three hospitalizations due to heart failure over the preceding year. Only 15 patients were included, and all underwent a nightly 12 h exchange regimen using 7.5% icodextrin solution. A control group was missing. After a follow-up of 24 ± 8 months, NYHA stages were improved and LVEF was preserved. The cumulative hospitalization time decreased from 8.9 ± 2.8 to 1.5 ± 1.2 days/month (P-values indicative for statistical significance).

The last study that needs to be mentioned was also published in 2019. Al-Hwiesh et al [43] performed a prospective trial in CRS type 1 including a total number of 88 patients. One half was assigned to receive either ultrafiltration treatment or tidal PD, respectively. The primary endpoint was a composite of serum creatinine and LVEF improvement. The study showed that ultrafiltration therapy was inferior to tidal PD, not only regarding the primary endpoint but also regarding the tolerability. Adverse events occurred more frequently in the ultrafiltration group ($P < 0.007$).

Rao and colleagues evaluated an exciting approach for sodium removal, the intraperitoneal administration of sodium-free 10% dextrose (DSR). The authors performed porcine experiments in which 1 L DSR solution efficiently removed sodium within a short period (4.1 ± 0.4 g sodium in 2 h). The effects on serum electrolytes were minor. Initial experiments on humans were performed also, and the tolerability was well [44]. Future systematic studies must show the efficacy of the procedure in refractory hypervolemia due to impaired cardiac/kidney function.

The currently available data indicate PD as an effective therapeutic option for fluid removal in refractory heart failure ± kidney dysfunction. However, it remains difficult to compare studies due to several reasons: 1) the heterogeneity of the study designs; 2) the lack of control groups in many investigations; and 3) the heterogeneity of procedures used for treatment (nocturnal versus daily PD, intermittent versus non-intermittent daily PD, composition of PD solution).

Non-PD KRT

Regarding hemodialysis therapy, two transport processes, responsible for fluid and solute removal must be distinguished: diffusion and ultrafiltration including convection. Diffusive solute transport is the predominant mechanism of solute elimination in hemodialysis. To eliminate water, a pressure gradient between blood (patient) and dialysis solution (machine) determines the net movement of water per time. This process, termed ultrafiltration, also results in the depletion of solutes, which are eliminated from the blood via convection. Thus, nephrologist distinguish between three extracorporal procedures: pure hemofiltration (exclusive ultrafiltration - rarely performed in dialysis units today), hemodialysis (solute removal is mediated by diffusion more than by ultrafiltration), and hemodiafiltration (comparably mediated solute by diffusion and ultrafiltration). Today, nephrologists perform hemodialysis or hemodiafiltration using standardized dialysis machines. In recent years,

several studies on refractory heart failure evaluated the efficacy of so-called "aquapheresis" [45]. In some trials, the net elimination of water was even achieved by certain machines such as the Aquadex System 100 (CHF Solutions®). It needs to be realized that aquapheresis is by no means a new therapeutic technique. Water is eliminated by ultrafiltration, therefore aquapheresis may more or less be regarded as hemofiltration. Nevertheless, studies that evaluated aquapheresis in CRS emphasize the fact that solute elimination is almost absent.

Leskovar and colleagues [46] published a retrospective, uncontrolled, observational cohort study, including the following subjects: refractory chronic heart failure with preserved or reduced ejection fraction ± CKD stages 3-4. Therefore, subjects with CKD were to be classified as CRS type 3. Patients received hemodialysis therapy, which lowered the hospital readmission rate due to heart failure and shortened the annual duration of hospital stay. In addition, KRT significantly improved the 5-year survival as compared to the general NYHA 4 population.

In a Japanese study [47], two types of extracorporal KRTs were compared with each other: continuous veno-venous hemofiltration (CVVH) and slow continuous ultrafiltration (SCUF). The study by Premuzic and colleagues [47] was performed as a prospective trial, and the follow-up period was 24 months. Only subjects with CRS types 1 and 2 were included with 54 in the CVVH and 23 in the SCUF group, respectively. Overall, survival rates were higher in the CVVH group, particularly in patients with lower urine output and cardiomyopathy. The total treatment time was longer in the CVVH group (18.3 ± 6.1 vs. 10.8 ± 3.6 h; $P < 0.001$) but the ultrafiltration rate was lower (155 ± 7.1 vs. 250 ± 17.4 mL/h; $P < 0.001$). The authors concluded that CVVH is advantageous, most likely due to more effective removal of cytokines that act in a deleterious manner. However, the last conclusion was speculative only since serum cytokines were not measured at all.

The following four trials were performed using certain ultrafiltration techniques, occasionally termed as aquapheresis.

The RAPID-CHF trial was published by Bart and colleagues in 2005 [48]. Subjects underwent ultrafiltration, although the original manuscript does not offer detailed information about the machine used for water removal. The study was performed on patients with refractory congestive heart failure (CHF), but the term CRS was not used. A total number of 40 was included, one-half received standard or usual care, and the second half underwent usual care plus ultrafiltration. The latter was performed only once, and the endpoint was weight reduction at 24 h after inclusion. Fluid removal was about 4,600 mL in the ultrafiltration group versus about 2,800 mL in the usual care group. Extracorporal treatment was tolerated satisfactorily.

In 2012, the same lead author published the CARRESS-HF investigation [49]. Fluid removal was achieved with a specific ultrafiltration system. The study was performed in CRS type 1. One hundred and eighty-eight patients (188) were randomly assigned to receive either ultrafiltration or drug therapy. Primary endpoints were changes in serum creatinine and body weight at 96 h. Ultrafiltration was inferior with regard to the composite endpoint delta serum creatinine and body weight loss. While the latter did not differ between the two groups, serum creatinine significantly increased as a result of aquapheresis. In addition, extracorporal treatment was associated with a higher rate of side effects.

The CUORE trial was published in 2014 [50]. It did not exclusively consider subjects diagnosed with CRS but patients with severe CHF. The principal aim was to compare standard (drug-based) therapy with ultrafiltration as respective first-line treatment. Weight reduction was comparable in the two groups (standard treatment 7.5 ± 4.5 kg and ultrafiltration 7.9 ± 5.0 kg). However, the rehospitalization rate was lower in subjects that received ultrafiltration. In addition, extracoporal therapy was associated with a more stable kidney function and lower natriuretic peptide levels in the blood.

The AVOID-HF trial [45] finally was performed in patients with decompensated heart failure again, and the exclusive diagnosis of CRS was omitted. Nevertheless, the study is of significant interest since so-called aquapheresis was employed for volume depletion. The study was designed multicentric and prospective, and a total number of more than 800 subjects were intended to be included. The trial was prematurely terminated by the sponsor since unwanted side effects occurred significantly more often in the ultrafiltration group. Two hundred and twenty-four patients were included before termination. Subjects that received ultrafiltration showed fewer cardiovascular events and a longer period until the next heart failure event. Almost 10 years earlier, the same leading author (Costanzo et al [51]) had published a study performed on 200 heart failure patients (ejection fraction below 40%) that received ultrafiltration in comparison to intravenous diuretic therapy. Volume depletion and rehospitalization improved significantly better under ultrafiltration, and the tolerability did not differ between the two groups.

The previous studies are heterogenous in several aspects. Firstly, not all trials were exclusively performed in CRS. Secondly, the respective endpoints and follow-up periods differed significantly. For instance, Bart and colleagues [48] evaluated the tolerability of extracorporal volume depletion in comparison to conventional (diuretics) therapy, and weight reduction was measured only once, 24 h after inclusion. The latest mentioned study by Costanzo et al [45] in contrast defined a follow-up period of 90 days. Thirdly, and this aspect is quite important, the technical procedures used for volume depletion were by no means comparable. They included conventional hemodialysis [46], CVVH and SCUF [47], and the respective methods used for "pure" ultrafiltration including aquapheresis. In order to decide whether extracorporal therapy may be applicable in drug-resistant heart failure not only in the short but also in the long term, future study designs need to be harmonized: 1) A "mixture" of the different types of CRS should be avoided. 2) The respective procedures used for volume (and sodium) depletion must be defined and unitized. The fact that "aquapheresis" has more or less been discussed as a "new" technique suitable for volume elimination reflects at least the lack of an integrative cardiorenal approach to the patient. Ultrafiltration has been performed by nephrologists all over the world ever since. 3) Endpoints must be defined for both, the short- and the long term.

Table 1 summarizes the studies discussed above [4-6, 32-38, 40-51].

Table 1. Summary of Studies Related to PD and Non-PD KRT in Congestive/Refractory Heart Failure and in Different Types of CRS

Reference	Design	Results
PD		
Al-Hwiesh et al, 2019 [43]	Prospective, CRS type 1, ultrafiltration versus tidal PD	Tidal PD superior with regard to primary endpoint and tolerability
Bertoli et al, 2014 [38]	Retrospective, multicentric, refractory heart failure, PD regimens differed significantly between study sites, no control group	Reduction of hospitalization time due to heart failure
Cairns et al, 1968 [32]	PD performed in 16 subjects with refractory heart failure, no control group	Substantial volume depletion in 12 subjects
Chopra et al, 1970 [33]	Case study series in four subjects with refractory pulmonary edema due to myocardial infarction	Recompensation in three individuals
Grossekettler et al, 2019 [41]	Retrospective cohort study, refractory heart failure, no control group	Improvement of the NYHA stage and of hospitalization due to decompensation
Koch et al, 2012 [37]	Prospective, refractory heart failure NYHA stages 3 + 4 and CKD, nocturnal PD, 12 h per night, no control group, follow-up about 1 year	Survival 77%, 71%, and 55% at months 3, 6, and 12; age, diabetes mellitus, serum urea, and brain natriuretic peptide associated with mortality
McKinnie et al, 1985 [34]	Case study in refractory heart failure	Prolonged control of volume status over 2 years
Pavo et al, 2018 [4]	Prospective, refractory right heart failure, no control group	Number of hospitalizations declined; extended ascites, better residual renal function, and no help needed in performing PD were beneficial
Ponce et al, 2017 [5]	Prospective, CRS type 1, high-volume PD with targeted Kt/V (0.5), no control group	Age, ACS and positive fluid balance associated with mortality
Rao et al, 2020 [44]	Experimental porcine study, sodium-free dextrose solution for sodium elimination; proof-of-concept in humans	Effective sodium elimination with almost no effect on serum electrolytes; tolerability in humans well
Rubin and Ball, 1986 [35]	Case study series in refractory heart failure	Prolonged control of volume status in eight subjects
Shao et al, 2018 [40]	Prospective, CRS type 2 and other CRS, follow-up until death or PD discontinuation, no control group	CRS type 2 identified as independent risk factor for death
Tormey et al, 1996 [36]	Case study series, intermittent ambulatory in refractory heart failure	Follow-up period of 18 ± 10 months, reduction of in-hospital time and NYHA stage improvement from IV to II
Wojtaszek et al, 2019 [42]	Prospective, refractory heart failure, no control group, follow-up 24 ± 8 months	NYHA stages improved, preserved left ventricular ejection fraction, decrease of cumulative hospitalization time
Xue et al, 2019 [6]	Retrospective cohort study; groups: non-CRS, acute heart failure, CRS type 2 and 4	All types of CRS were not associated with mortality; CRS type 4 alone was
Non-PD KRT		
Bart et al, 2005 [48]	RAPID-CHF trial, prospective, refractory heart failure, ultrafiltration - procedure not specified in detail, control group received drug therapy only, evaluation of subjects at 24 h after therapy initiation	Fluid removal about 4,600 mL in the ultrafiltration group versus about 2,800 mL in the control group; ultrafiltration well tolerated
Bart et al, 2012 [49]	CARRESS-HF trial, prospective, CRS type 1, control group received drug therapy only, so-called aquapheresis	Ultrafiltration inferior with regard to the composite endpoint delta serum creatinine and body weight loss; more side effects in the ultrafiltration group
Costanzo et al, 2007 [51]	Prospective, hypervolemic heart failure with left ventricular ejection fraction < 40%, ultrafiltration versus intravenous diuretic therapy	Ultrafiltration mediates more efficient volume depletion and reduces rehospitalization rate
Costanzo et al, 2016 [45]	AVOID-HF trial, prospective, multicentric, aquaphereses versus drug therapy	Study terminated prematurely due to higher rate of side effects in the aquapheresis group

Table 1. Summary of Studies Related to PD and Non-PD KRT in Congestive/Refractory Heart Failure and in Different Types of CRS - *(continued)*

Reference	Design	Results
Leskovar et al, 2017 [46]	Retrospective cohort study, refractory HF-REF or HF-PEF ± CKD stage 3 + 4, conventional hemodialysis, no control group	Lower hospital readmission rate, shortening of the annual duration of hospital stay, improved 5-year survival (as compared to the general NHYA stage 4 population)
Marenzi et al, 2014 [50]	CUORE trial, prospective, congestive heart failure, ultrafiltration versus drug therapy as first-line treatment	Rehospitalization was lower in subjects receiving ultrafiltration; extracoporal therapy associated with better renal outcome
Premuzic et al, 2017 [47]	Prospective, CRS types 1 and 2, CVVH versus SCUF, follow-up 24 months, no control group	Higher survival rates in CVVH-treated subjects

KRT: kidney replacement therapy; CKD: chronic kidney disease; CRS: cardiorenal syndromes; ACS: acute coronary syndrome; CVVH: continuous veno-venous hemofiltration; HF-PEF: heart failure preserved ejection fraction; HF-REF: heart failure reduced ejection fraction; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PD: peritoneal dialysis; SCUF: slow continuous ultrafiltration.

KRT in CRS Type 5: Septic AKI

CRS type 5 encompasses different disorders that simultaneously affect both heart and kidney. The most "prominent" syndrome, however, is sepsis. The topic "KRT in septic AKI" is extensive to say the least. It seems therefore appropriate to refer to the latest "S3 Guideline Sepsis - prevention, diagnosis, therapy, and aftercare" [52]. It proposes to initiate KRT in septic AKI with either intermittent or continuous procedure. The reason for not providing a more distinct recommendation for one procedure over the other simply results from the fact that studies performed so far failed to prove the significant superiority of any procedure. Some trials indicated the superiority of continuous KRT [53, 54], while others did not confirm these findings [55]. A more detailed discussion of the topic "KRT in septic AKI" was, without doubt, possible in a separate article.

Conclusions, Problems, and Perspective

The data available so far allow the following conclusions: dialysis, including PD and the heterogeneous group of non-PD KRT, control hypervolemia in different types of CRS and in refractory heart failure ± kidney excretory dysfunction in an effective manner. The safety depends on the respective procedure used. Future studies should be designed in order to reduce/avoid the following problems: 1) Evaluation of different types of CRS in the same trial. 2) The lack of a control group. 3) Choosing dialysis treatment characteristics according to study site-related protocols if the study is multicentric. 4) No study so far compared PD with non-PD KRT in CRS or in refractory heart failure alone. This topic should be addressed.

Finally, the general awareness of physicians, particularly of nephrologists toward CRS, may still be limited. A relevant number of patients treated in dialysis units all over the world require KRT most likely due to CRS. For many years, dialysis dependency has either been attributed to CKD or to persistent AKI. By expanding the interdisciplinary understanding of kidney diseases, starting already during the early training of physicians at universities, the significance of CRS will become more obvious. This will allow to perform a greater number of systematic analyzes and to decide which KRT mode is to be preferred in which type of CRS.

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Conflict of Interest

The authors have no conflict of interest to disclose.

Author Contributions

DP wrote the manuscript. KD searched for literature and corrected the article. IM, BM, and SP provided additional references and corrected the article. OR corrected the article.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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