Peritoneal ultrafiltration in end-stage chronic heart failure

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Abstract

Background. Cardiorenal syndrome type 2 (CRS-2) is common in end-stage chronic heart failure (CHF). Peritoneal ultrafiltration (pUF) may entail clinical functional improvement and a reduction in hospitalizations.

Methods. Thirty-nine consecutive end-stage CHF patients with stable CRS-2 were initiated on ambulatory pUF after interdisciplinary cardiological/nephrological evaluation and prospectively followed for 1 year. All-cause hospitalization was the primary end point. Secondary end points included mortality, treatment alteration and change in weight, NYHA functional class or quality of life (QoL). Outcomes were compared both within the pUF cohort (365 prior to initiation) and with 39 matched CHF patients receiving standard medical treatment.

Results. Compared with pretreatment, there was a trend to a reduction in 1-year hospitalization days in the pUF group (P = 0.07). One-year mortality was 33% in the pUF group and 23% in the matched control cohort. pUF was stopped in eight patients (18%) due to recurrent peritonitis (n = 3), insufficient ultrafiltration (n = 3) or cardiac recompensation (n = 1). Compared with standard medical treatment, pUF significantly improved volume overload (P < 0.05), NYHA functional class (P < 0.001) and mental health (P < 0.05). Moreover, hospitalization days for all causes as well as cardiovascular hospitalization days were significantly reduced during the interim periods in the pUF group (P < 0.05 and P < 0.001, respectively).

Conclusions. pUF is effective in improving the clinical condition of end-stage CHF patients suffering from CRS-2. Randomized controlled trials are needed to clarify the effects of pUF on hospitalization and mortality in these patients.

Keywords: cardiorenal syndrome; chronic heart failure; haemodialysis; hospitalization; peritoneal ultrafiltration

Introduction

Advanced chronic heart failure (CHF) often leads to a decline in renal function, a condition known as cardiorenal syndrome type 2 (CRS-2) [1]. Chronic kidney disease is present in up to 63% of CHF patients, and it is a powerful independent predictor of prognosis [2]. Possible pathophysiological mechanisms mainly relate to a reduced renal perfusion due to low cardiac output and renal venous congestion in patients with maintained cardiac output [3]. Consequently, patients develop diuretic-resistant fluid overload causing recurrent episodes of pulmonary congestion and oedema. This hypervolaemia then contributes to heart failure (HF) progression and mortality, leading to a 1-year mortality rate of up to 77% in advanced CHF and CRS-2 [4].

The effectiveness of pharmacological and device therapy in end-stage CHF is limited. Heart transplantation, left ventricular assist device implantation and other surgical procedures for patients refractory to optimal standard therapy are often not suitable due to a high comorbidity or advanced age of these patients. Thus, alternative treatment strategies are urgently needed.

Peritoneal ultrafiltration (pUF) may allow chronic treatment of diuretic resistance by providing continuous ultrafiltration without the need of central venous access or hospital admission [5]. In fact, several small studies described clinical improvements, and a reduction in hospitalization rates in end-stage CHF patients treated with pUF, with the first case report being published by Schneier et al. in 1949 [6–15]. More recently, these findings were confirmed in two cohorts of 118 and 126 end-stage HF patients, respectively [16, 17].

There are, however, no randomized trials addressing this subject and none of the above-listed studies directly compared pUF therapy with standard treatment of advanced CHF.
CHF and CRS-2. Furthermore, while complication rates are well described for pUF in general, very little is known about whether the presence of severe CHF alters both types and rates of these complications. We therefore sought to prospectively evaluate the effects of pUF therapy on the morbidity of refractory end-stage CHF patients and to compare outcomes with matched CHF patients who received optimal standard therapy.

Materials and methods

Patient selection

Treatment group. Between 2006 and 2012, patients with end-stage CHF were initiated on ambulatory pUF after interdisciplinary cardiological/nephrological assessment under the following conditions: (i) individually optimal pharmacological therapy, (ii) device therapy as indicated by guidelines [18], (iii) recurrent cardiac decompensation defined as at least two hospitalizations within the last 6 months, (iv) diuretic resistance defined as refractory hypertension despite optimal sequential diuretic therapy and (v) not suitable for heart transplantation.

CHF was established according to current guidelines [18]. Patients on inotropic support and those with an implanted cardiac assist device were excluded from this study. Renal function was assessed using the Modification of Diet in Renal Disease (MDRD) equation. Volume/hydration status, lean tissue mass and fat mass were measured via bioimpedance (Body Composition Monitor, Fresenius Medical Care, Bad Homburg, Germany). Patients already depending on renal replacement therapy due to advanced renal failure were excluded.

After implantation of a peritoneal Tenckhoff catheter, patients were instructed to perform pUF either as continuous ambulatory peritoneal dialysis (CAPD) or as automatic peritoneal dialysis (APD). Subsequently, patients were attended to at the nephrology outpatient clinic during scheduled visits every 4–6 weeks. All visits included assessment of patient history, physical examination, weight, laboratory measurements and medication.

All patients were asked to provide written informed consent to storage of their clinical data in a web-based registry and use thereof for research purposes. Inclusion into the registry is prospective, continuous and ongoing. Obtained clinical data at study visits included patient history, physical examination, weight, BMI (body mass index), laboratory measurements and medication. In addition, quality of life (QoL) was assessed using the SF-36 questionnaire.

Control group. Patients of the control group were selected from the Heidelberg Heart Failure Registry. All patients attending the HF outpatient clinic of the University of Heidelberg for the evaluation of HF were asked to provide written informed consent for their data to be recorded and used for research purposes. Inclusion into the Heidelberg Heart Failure Registry is continuous and ongoing. Clinical data include patient history, symptoms, physical examination, echocardiography, exercise testing, laboratory measurements and medication. Medication is at the discretion of the referring physician with respect to guideline recommendations. The proceedings of the registry confirm to the Declaration of Helsinki and were approved by the Ethics Committee of Heidelberg.

Matching. We retrospectively identified end-stage CHF patients from our Heidelberg Heart Failure registry and matched them to pUF patients with respect to age, NYHA functional class and MDRD. Patient follow-up (including determination of survival status) of the control group was achieved by scheduled visits to the outpatient clinic, or by telephone calls either to the patient’s home or to their physician, or by electronic hospital records.

End points

All-cause hospitalization was the primary end point of this study. Secondary end points included all-cause mortality, alteration of renal replacement therapy, weight loss, NYHA, renal function and QoL. Patients who stopped pUF therapy were followed until treatment change and censored thereafter. Being a planned procedure, hospitalization for implantation of the peritoneal Tenckhoff catheter at initiation of pUF was not factored into the analysis.

Statistics

The data are presented as mean ± SD, median [inter-quartile range] or number (%). To compare frequencies, \( \chi^2 \) analysis was performed. To test for significant differences between groups, the two-sample Wilcoxon test and Student’s t-test were used where appropriate. Survival curves of patients were generated by the Kaplan–Meier method.

All-cause hospitalization, all-cause mortality, alteration of renal replacement therapy, weight loss and NYHA were compared (i) within the pUF cohort and the control group, respectively, and (ii) between groups. QoL was compared between treatment groups.

All tests are two-tailed and an arbitrary P-value of <5% was regarded as statistically significant.

Results

Study cohorts and follow-up

A total of 54 end-stage CHF patients were initiated on pUF. Of these, 39 patients were followed for at least 3 months and therefore included into this analysis (pUF cohort). Consequently, 39 end-stage CHF patients were identified in the Heidelberg Heart Failure Registry and matched to pUF patients with respect to age, NYHA and MDRD (control cohort). At initiation of pUF or inclusion into the control cohort, all patients suffered from NYHA Class III or IV symptoms. Mean left ventricular ejection fraction was 24 ± 7% in the pUF cohort and 27 ± 12% in the matched cohort (P = 0.29). Median estimated glomerular filtration rate (eGFR) was <30 mL/min/1.73 m² in both cohorts, indicating severe concomitant renal disease. As shown in Table 1, baseline characteristics were well balanced between cohorts. Actual follow-up for all patients starting pUF treatment was 6 (6–16) months, and follow-up time in the matched control group was 12 (7–14) months.

Primary end point

The number of hospital admissions as well as hospitalization days in the 12 months prior to study inclusion did not differ between pUF patients and those in the matched control group [3 (2–4) versus 3 (1.5–3.5), P = 0.38, and 30 (12–58) versus 16 (8–69), P = 0.52, respectively]. When
Mortality. Versus 2 (1.5–3.5) times, P = 0.99.

Secondary end points
Mortality. One-year all-cause mortality was 33% (n = 13) in the pUF group and 23% (n = 9) in the matched control group (P = 0.31). Cumulative survival of pUF-treated patients is shown in Figure 2.

Alteration of renal replacement therapy. During the first year of follow-up, seven patients (18%) stopped pUF and started haemodialysis. Reasons for treatment alterations were insufficient pUF (n = 3) and recurrent peritonitis (n = 3). For one patient, the cause of treatment alteration was not reported. One patient ceased renal replacement therapy because of cardiac recompensation. In three patients, follow-up was shorter than 12 months, and no end point was reached during their follow-up period. One year after initiation of pUF, 18 patients (46%) were still treated with pUF (Figure 3). Cumulative event-free survival curves of end-stage CHF patients treated with pUF are shown in Figure 4.

Weight loss. Patients on pUF significantly decreased their body weight, reflecting reduced volume overload. This effect was detectable after 3 months of treatment (81 ± 14 versus 77 ± 13 kg; P < 0.001) and persisted to the end of follow-up (81 ± 14 versus 78 ± 13 kg; P < 0.05). Overhydration estimated by bioimpedance measurement was 3.5 (2.5–5.7) L at baseline and decreased to 2.6 (1.2–3.5) L at the end of follow-up (P < 0.05). Fat mass, on the contrary, was unchanged after 3 months [32 (25–38) versus 32 (27–40) kg, P = 0.63] but significantly increased at the end of follow-up [32 (25–38) versus 39 (32–47) kg, P < 0.01]. Clinical characteristics of pUF patients at baseline, after 3 months and at the end of follow-up are presented in Table 2.

Patients in the matched control group showed no reduction of body weight at follow-up (81 ± 23 versus 75 ± 16 kg; P = 0.44). Bioimpedance measurements were not available for these patients (Table 3).

NYHA functional class. Patients treated with pUF significantly improved their NYHA class during follow-up (P < 0.001). Patients in the matched control group also clinically improved (P < 0.0001, P = 0.79; for within the matched control group and between group comparison, respectively).

Renal function. Three months after initiation of pUF therapy, renal function expressed as eGFR was stable, but it significantly decreased in the further course from 20 (14–26) to 16 (11–20) mL/min/1.73 m² at Vlast (P = 0.048) compared to pretreatment. In addition, urinary volume tended to decrease, while the amount of pUF significantly increased (Table 2). The amount of pUF significantly correlated with the patient's urinary volume after 3 months of pUF treatment (r = 0.538; P = 0.003), but it did not correlate at the time of last available follow-up (r = 0.342; P = 0.12). There was no correlation between the amount of pUF and eGFR neither at V1 (r = 0.282; P = 0.17) nor at Vlast (r = 0.0009; P = 0.99).

Quality of life. QoL was assessed using the SF-36 questionnaire. QoL measures after initiation of pUF were compared with those of the matched control group. Patients on pUF tended to report a better QoL regarding the subscales 'mental health' (SF-36 score 52 versus SF-36 score 69, P < 0.05) and 'vitality' (SF-36 score 26 versus SF-36 score 40, P = 0.07). There was no difference in QoL between women and men.

Discussion
The present study addresses the effects of pUF therapy on the morbidity of end-stage CHF patients suffering from CRS-2. Our main findings are as follows:

- Compared with pretreatment, there was a trend towards a reduction in the number of 1-year hospital admissions in patients on pUF.
- Compared with pretreatment, there was a significant decrease of hospitalization days both for all-cause as well as cardiovascular hospitalization days in patients on pUF.
- pUF therapy significantly improved volume overload and NYHA class.
Residual renal function and urinary volume significantly decreased during pUF treatment. Patients on pUF reported a better QoL compared with the matched control group. One-year mortality of end-stage CHF patients treated with pUF was 33%.

As therapeutic options for end-stage CHF patients refractory to pharmacological treatment are scarce, the role of new treatment strategies such as pUF needs clarification. Current guidelines propose ultrafiltration or haemofiltration as beneficial methods in diuretic-resistant CHF. However, there is no further specification of patient selection, treatment modality and expected outcome due to a lack of randomized controlled trials [18, 19].

Already for acutely decompensated HF, the role of extracorporeal ultrafiltration is discussed controversially: while some found it to be effective in reducing volume overload and 90-day HF hospitalization [20], others could not reproduce the benefits while reporting a higher incidence of adverse events [21]. Compared with extracorporeal modalities, pUF as an intracorporeal treatment offers device-specific advantages such as continuous ultrafiltration, fluid removal from the non-vascular space and avoidance of a compensatory increase of sympathetic activity. Therefore, pUF might be an attractive therapeutic alternative in patients with refractory severe HF, in which other alternatives might not be appropriate.

Consequently, pUF has been studied in patients with refractory severe HF in a number of case reports, small observational and two large retrospective studies [6–9, 14–17, 22–24]. They mainly report an improvement in NYHA class and a reduction of volume overload after initiation of pUF treatment [8–11, 13–16, 22].

In addition to the fact that we were able to reproduce positive effects on volume control, the number of all-cause hospitalization days as well as cardiovascular hospitalizations significantly decreased in the pUF cohort. This

![Fig. 1. Hospitalization 12 months prior to study inclusion and at 12 months follow-up. (a) number of hospital admissions within the pUF group, (b) number of hospital admissions within the control group, (c) hospitalization days within the pUF group, (d) hospitalization days within the control group and (e) cardiovascular hospitalization days within the pUF group.](image1)

![Fig. 2. Kaplan-Meier curve of 1-year survival in CHF patients treated with peritoneal ultrafiltration.](image2)
Peritoneal ultrafiltration in end-stage CHF

is in accordance with previous data on all-cause hospitalization [14, 22] and cardiovascular hospitalization [7, 8, 11, 15, 17] in comparable to CHF cohorts. Possible reasons for the non-significant reduction of hospital admissions may be the small study cohort and the incidence of complications: in our study, 18% of pUF-treated patients switched to haemodialysis during follow-up, mainly due to technical complications. The rate of pUF complications described in other studies varies between 0.053 and 0.75 episodes of peritonitis per patient and year [8, 11, 16]. Thus, the relatively high incidence of insufficient ultrafiltration and recurrent peritonitis may in part have counteracted the positive effects of pUF on volume control and cardiac function. However, in light of a highly morbid patient cohort suffering from end-stage CHF, even a stabilization of the rate of hospital admissions reflects a substantial benefit.

In line with previous reports [8, 11, 14], patients treated with pUF reported a better QoL than patients in the matched control group. Interestingly, mental health rather compared with physical health improved. This may be due to the close medical monitoring of pUF patients.

There is ongoing debate whether haemodialysis represents a better means of fluid control over pUF. Smaller studies did not detect any differences between treatment strategies [8], while a retrospective study on 23 718 incident dialysis patients found pUF to be associated with 48% lower mortality than haemodialysis over the first 2 years of dialysis therapy [25]. Registry data on the other hand indicate that mortality risk might be higher with pUF than with haemodialysis among incident patients with end-stage renal disease and CHF [26, 27]. These registry data were criticized both for imprecise characterization of CHF and imbalance of severity of CHF while all patients required renal replacement therapy as a result of end-stage chronic kidney disease. Thus, results may not be comparable to our cohorts and/or be transferable to end-stage CHF suffering from CRS-2 in general.

Our study highlights some very important aspects with respect to study design of pUF studies. Even though within-patient comparison appears promising, it does not account for two confounders: (i) during observation, the natural course of the disease (both CHF and CRS-2) alters the rate of end points for each (sequential) observational period, and (ii) the intensified follow-up after pUF initiation might bias non-pUF treatment intensity and thus morbidity. We are the first to address these issues through identification of a matched cohort.

This match, however, can only account for the severity of CHF itself but not for the extent of the cardiorenal syndrome. This is due to the fact that if the matched patients had presented with equally severe CRS-2, they would have been initiated on pUF. Consequently, patients in the pUF group were likely to suffer from more advanced HF than patients in the matched control group. This is also reflected in higher NTproBNP and blood urea nitrogen (BUN) levels in the pUF group compared with the matched control group. BUN on the other hand is an independent predictor of short-term [28] and long-term [29] mortality in CHF.

Reported 1-year mortality for patients on pUF varies between 18 and 45% [14, 16] compared with ~45% for patients with end-stage CHF in epidemiologic studies [30]. Correspondingly, 1-year mortality in our cohort was 33% in the pUF group and 23% in the matched control group. Our interpretation, though, is not that of a seeming non-inferiority of pUF. In light of the above differences of disease severity, we would rather consider the equalization of the net mortality risk of these more severely ill patients to that of patients without CRS-2 as a clear net benefit.

Ultimately, the potential benefit of pUF in CRS-2 can only be adequately addressed in a randomized trial.
Table 2. Characteristics of pUF-treated patients at study inclusion (V0), after 3 months (V1) of treatment and at last available follow-up (Vlast)

| V0 | V1 | P-value (V0 versus V1) | Vlast | P-value (V0 versus Vlast) |
|----|----|------------------------|-------|--------------------------|
| Months after V0 | 3 | 6 (6–16) | | <0.05 |
| Dialysis mode, n | | | | |
| CAPD | 21 | | | |
| APD | 17 | | | |
| HD | 1 | 9 | | |
| Age, years | 67 ± 11 | 67 ± 11 | | 68 ± 11 | | |
| Weight, kg | 81 ± 14 | 77 ± 13 | <0.001 | 78 ± 13 | <0.05 |
| BMI, kg/m² | 26 ± 4 | 26 ± 4 | 0.63 | 27 ± 4 | 0.44 |
| LVEF, % | 24 ± 7 | 26 ± 9 | 0.62 | 30 ± 12 | 0.10 |
| NYHA | 3.6 ± 0.5 | 2.9 ± 0.7 | <0.001 | 2.8 ± 0.6 | <0.001 |
| I, n (%) | 0 (0) | 0 (0) | | 1 (3) | |
| II, n (%) | 0 (0) | 4 (10) | | 5 (13) | |
| III, n (%) | 18 (46) | 17 (44) | | 16 (41) | |
| IV, n (%) | 21 (54) | 2 (6) | | 3 (8) | |
| SBP, mmHg | 116 ± 21 | 112 ± 20 | 0.37 | 110 ± 24 | 0.25 |
| DBP, mmHg | 70 ± 14 | 61 ± 11 | <0.01 | 62 ± 13 | <0.01 |
| Exchanges (CAPD patients), n per day | | | | |
| ≤2 | 5 | | 4 | 0.70 |
| >3 | 11 | | 14 | |
| APD volume, mL per day | 10 250 (11 000–12 075) | 11 300 (10 500–15 250) | 0.20 | | |
| NTproBNP, pmol/L | 1237 (658–2403) | 1259 (616–2611) | 0.30 | 1892 (1099–3124) | 0.10 |
| Potassium, mmol/L | 4.5 ± 0.8 | 4.3 ± 0.7 | 0.16 | 4.3 ± 0.6 | 0.19 |
| Sodium, mmol/L | 137 ± 6 | 137 ± 6 | 0.63 | 136 ± 5 | 0.45 |
| Hb, g/dL | 6.8 ± 1.2 | 7.1 ± 1.3 | 0.13 | 6.8 ± 1.2 | 0.79 |
| CRP, mg/L | 9 (4–19) | 5 (2–13) | 0.08 | 10 (5–16) | 0.67 |
| Albumin, g/L | 40 ± 4 | 37 ± 4 | <0.01 | 36 ± 6 | <0.01 |
| Phosphate, mmol/L | 1.4 ± 0.5 | 1.5 ± 0.6 | 0.65 | 1.6 ± 0.6 | 0.48 |
| eGFR, mL/min/1.73 m² | 22 (16–30) | 20 (14–26) | 0.74 | 16 (11–22) | 0.048 |
| Creatinine, µmol/L | 230.1 (185.9–327.5) | 265.5 (221.3–336.3) | 0.09 | 300.9 (239.0–451.4) | <0.01 |
| BUN, mmol/L | 232 (170.0–314.4) | 184 (130.0–215.1) | <0.01 | 170 (105.0–217.7) | <0.001 |
| Overhydration, L | 3.5 (2.1–5.1) | 2.8 (1.8–3.5) | 0.10 | 2.6 (1.2–3.5) | <0.05 |
| Peritoneal ultrafiltration, mL | 1950 (1500–2350) | 1250 (725–1900) | 2000 (1548–2350) | <0.001 |
| Urinary volume, mL | 1250 (725–1900) | 650 (288–1875) | 0.07 | | |
| Kt/V | 2.05 (1.62–2.85) | 2.00 (1.40–2.30) | <0.001 | | |
| Lean tissue mass, kg | 41 (34–46) | 38 (32–46) | 0.43 | 33 (29–44) | <0.05 |
| Fat mass, kg | 32 (25–38) | 32 (27–40) | 0.63 | 39 (32–47) | <0.01 |
| ACEI/ARB, n (%) | 27 (69) | 22 (56) | 0.06 | 18 (46) | <0.01 |
| Beta blocker, n (%) | 35 (90) | 32 (82) | 0.18 | 30 (77) | 0.06 |
| Spironolactone, n (%) | 17 (44) | 17 (44) | 1.0 | 12 (31) | 0.37 |

Values shown are mean ± SD or median (inter-quartile range). P-values <0.05 are written in italics.

Table 3. Characteristics of the matched control group at study inclusion (V0) and follow-up (Vlast)

| V0 | Vlast | P-value |
|----|-------|---------|
| Follow-up, months | 3.5 ± 0.5 | 2.6 ± 0.7 | <0.0001 |
| NYHA | 21 (7–14) | | |
| I, n (%) | 0 (0) | | |
| II, n (%) | 0 (0) | | |
| III, n (%) | 19 (49) | 7 (18) | |
| IV, n (%) | 20 (51) | 0 (0) | |
| Weight, kg | 82 ± 23 | 75 ± 16 | 0.43 |
| BMI, kg/m² | 29 ± 8 | 27 ± 6 | 0.68 |
| eGFR, mL/min/1.73 m² | 26 (19–32) | 30 (13–43) | 0.59 |
| BUN, mmol/L | 16.4 (12.8–26.6) | 13.4 (8.2–19.7) | 0.13 |
| NTproBNP, pmol/L | 576 (326–1457) | 721 (133–1228) | 0.62 |
| Potassium, mmol/L | 4.4 ± 0.6 | 4.3 ± 0.5 | 0.47 |
| Sodium, mmol/L | 138 ± 3 | 137 ± 3 | 0.81 |
| Hb, g/dL | 7.3 ± 1.0 | 7.7 ± 1.0 | 0.21 |
| CRP, mg/L | 6 (2–12) | 8 (2–21) | 0.90 |

Values shown are mean ± SD or median (inter-quartile range). NYHA: New York Heart Association functional class; BMI, body mass index; eGFR, estimated glomerular filtration rate using the Modification of Diet in Renal Disease equation; BUN, blood urea nitrogen; Hb, haemoglobin; CRP, C-reactive protein.

Limitations

The number of patients studied in this trial was limited which may hinder adequate statistical analysis. Moreover, data for the complete follow-up period were not available for all patients. Patient selection may have been biased because recruitment depends on whether or not the referring physicians deemed their patients suitable for this care.

Conclusion

Our results show that pUF is effective in improving the clinical condition of end-stage CHF patients suffering from CRS. Randomized controlled trials are needed to clarify the effects of pUF therapy on hospitalization and mortality in these patients.

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