Dialysis Therapy for Volume Overload: A Feasible Option to Reduce Heart Failure Hospitalizations in Advanced Heart Failure

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ABSTRACT **Background:** Advanced heart failure (HF) carries a high rate of recurrent HF hospitalizations and a very high mortality rate. Mechanical devices and heart transplantation are limited to a select few. Dialysis may be a good alternative for advanced HF patients with volume overload despite maximal pharmacological therapy.

Objectives: To assess the net clinical outcome of peritoneal dialysis or hemodialysis in patients with advanced HF.

Methods: We analyzed all advanced HF patients who were referred for dialysis due to volume overload in our institution. Patients were followed for complications, HF hospitalizations, and survival.

Results: We assessed 35 patients; 10 (29%) underwent peritoneal dialysis and 25 (71%) underwent hemodialysis; 71% were male; median (interquartile range) age was 74 (67–78) years. Estimated glomerular filtration rate was 20 (13–32) ml/min per 1.73 m^2. New York Heart Association functional capacity was III. Median follow-up time was 719 days (interquartile range 658–780). One-year mortality rate was 8/35 (23%) and overall mortality rate was 16/35 (46%). Three patients (9%) died during the first year due to line or peritoneal dialysis related sepsis, and 6 (17%) died during the entire follow-up. The median number of HF hospitalizations was significantly reduced during the year on dialysis compared to the year prior to dialysis (0.0 [0.0–1.0] vs. 2.0 [0.0–3.0], $P < 0.001$).

Conclusions: Dialysis is reasonably safe and significantly reduced HF hospitalization in advanced HF patients. Dialysis could be a good alternative for advanced HF patients with intractable volume overload.

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For editorial see page 480

Heart failure (HF) is a global health problem. HF carries a high rate of recurrent HF hospitalizations and a very high mortality rate [1]. Advanced HF is defined by the Heart Failure Association of the European Society of Cardiology as the end of the HF disease spectrum in which, despite optimal guideline-directed treatment, symptoms are persistent, severe cardiac dysfunction is present, and the patients have severe impairment of exercise capacity [2]. Mechanical devices and heart transplantation may be considered for these patients but are appropriate or available to only a small minority. Volume overload despite maximal diuretic therapy is a leading challenge in these patients, with a significant impact on quality of life. Diuretics are the mainstay of therapy for congestion. In advanced patients with chronic high-dose diuretic therapy, more than 20% of patients may demonstrate diuretic resistance [3], which is defined as failure to achieve effective congestion relief despite appropriate or escalating doses of diuretics.

Diuretic resistance may result from sub-therapeutic drug delivery to the distal tubule, drug interactions, compensatory mechanisms of distal tubule, and neurohormonal activation. This situation leads to frequent recurrent hospitalizations for decongestion. Dialysis may provide a therapeutic alternative for advanced HF patients with volume overload despite maximal pharmacological therapy. Several studies have evaluated this condition over the last few decades [4-10] suggesting that this modality can improve outcome in these severe patients, although this solution is not widely used. We assessed the net clinical outcome of chronic peritoneal dialysis or hemodialysis in patients with advanced HF.

PATIENTS AND METHODS

In this retrospective study, we analyzed all advanced HF patients who presented with severe congestive HF and were referred for dialysis due to volume overload at our institution in the period between 2014 and 2018. They were assessed to be in a hypervolemic state by at least two of the following criteria: peripheral edema; radiographic pulmonary edema or pleural effusion; enlarged liver or ascites; or pulmonary rales, paroxysmal

nocturnal dyspnea, speech dyspnea, or orthopnea. Patients were followed for HF hospitalizations, complications, and survival. The institutional committee for human studies of the Hadassah Medical Center approved the study protocol.

STATISTICAL ANALYSES

Statistical analyses were performed using Statistical Package for the Social Sciences software version 17 (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as median (quartiles) and categorical variables as counts (percentages). Comparison of the clinical characteristics was performed using the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. Follow-up time was calculated using Kaplan-Meier estimate of potential follow-up. Kaplan-Meier curves, with the log-rank test, were used to compare survival. Statistical significance was defined as $P < 0.05$.

RESULTS

PATIENT CHARACTERISTICS

We assessed 35 patients on dialysis for volume overload. The clinical characteristics of these patients are presented in Table 1. Ten patients (29%) underwent peritoneal dialysis and twenty-five (71%) hemodialysis. 71% were male; median (interquartile range [IQR]) age was 74 (67–78) years. Estimated glomerular filtration rate (eGFR) was 20 (13–32) ml/min per 1.73 m^2. New York Heart Association functional capacity was III and IV in 66% of the patients. Left ventricle ejection fraction (EF) at the time of commencement of dialysis included patients with EF > 50% (34%), EF 40–50% (22%), and EF < 40% (44%). The majority of patients (83%) were treated with maximally tolerated intravenous diuretics in an outpatient daycare setting in addition to optimal guideline-directed treatment prior to dialysis. In 19 patients (54%) the treatment with angiotensin converting enzyme inhibitors (ACE inhibitors) or angiotensin II receptor blockers (ARBs) was stopped because of worsening kidney function. The majority of the patients presented with significant valvular heart disease with at least moderate mitral regurgitation in 67% and at least moderate tricuspid regurgitation in 84%. Pulmonary hypertension with estimated systolic pulmonary artery pressure > 40 mmHg was present in 50% of the patients. Four patients (11%) (three on peritoneal dialysis and one on hemodyalisis) performed peritoneocentesis of ascites fluid in previous hospitalizations before the initiation of dialysis.

CLINICAL OUTCOME

Median follow-up time was 719 days (IQR range 658–780). One-year mortality rate was 8/35 (23%), the expected mortality rate in this advanced HF cohort [11]. Three patients (9%) died during the first year due to line or peritoneal dialysis related sepsis and 6 (17%) during the entire follow-up. Four patients (11%) died due to advanced heart failure during the entire follow-up, three of these patients during the first year after dialysis commencement. There was a marked reduction in HF hospitalizations after commencing dialysis. The median number of HF hospitalizations was significantly reduced during the year after dialysis compared to the year prior to dialysis (0.0 [IQR 0.0–1.0] vs. 2.0 [IQR 0.0–3.0], $P < 0.001$) [Figure 1]. Exclusion of patients who did not survive the first year demonstrated a very similar result with a significant reduction in HF hospitalizations following dialysis (0.0 [IQR 0.0–1.0] vs. 2.0 [IQR 0.0–3.0], $P < 0.001$, n=27). The median number of all-cause hospitalizations during the year following dialysis was also low (1 [IQR 0–3]).

DISCUSSION

The main finding of the present study is that dialysis is a practical option for advanced HF patients with intractable volume overload without other options. Dialysis significantly reduced HF hospitalization in these patients. Dialysis was also reasonably safe and the complication rate was acceptable. This therapy probably does not improve survival; however, it does reduce hospitalization rate, an important clinical goal in these patients.

The cardiorenal axis has been described well, with deterioration of one system seen in the setting of malfunction of the other. This bidirectional relationship is crucial in managing these patients as this relationship worsens congestion and volume overload [12]. Several studies have reported the association of venous congestion and decreased renal perfusion, leading to worsening renal function due to increased renal venous pressure. Increased central venous pressure is associated with decreased eGFR in patients with chronic HF [13]. In patients after ST-elevation myocardial infarction, the combination of elevated central venous pressure (CVP), and reduced left ventricular systolic function assessed by echocardiography was associated with the highest risk for acute kidney injury (AKI) [14]. This association suggests that acutely decompensated heart failure leads to AKI due to reduced effective renal blood flow secondary to venous congestion as well as acute reduction of cardiac output. This mechanism is classified as type 1 cardiorenal syndrome [15]. The cornerstone of treatment for volume overload is diuretics; however, diuretics increase neurohormonal levels, which causes electrolyte imbalance and may not control the volume overload. In the last several decades, a mechanical strategy to remove fluid has been evaluated as a feasible option for patients with advanced congestive HF, resistant to drug therapy in the acute setting, as well as in the chronic setting.

Ultrafiltration (UF) is an effective method of fluid removal with several potential advantages over diuretic-based approaches, including adjustable fluid removal volumes and rates, no effect on serum electrolytes, and decreased neurohormonal activity [16]. Several studies were performed to evaluate its effectiveness in the acute setting of decompensated HF [16-19]. While UF was

Table 1. Clinical characteristics of the patients

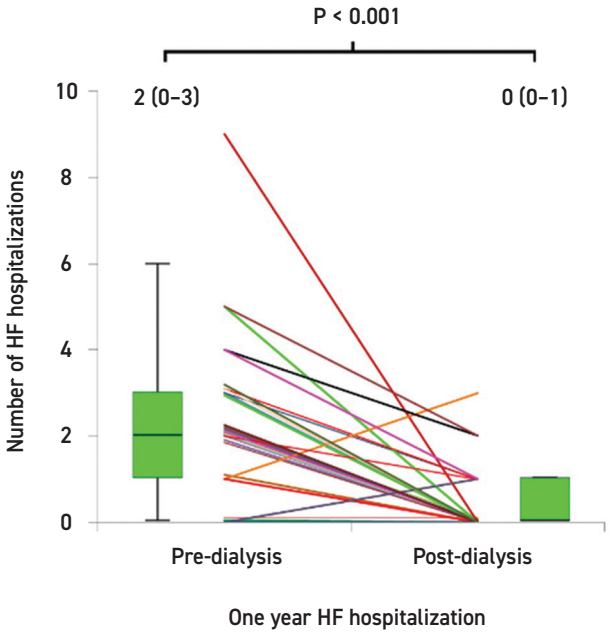
	Hemodialysis (n=25)	Peritoneal dialysis (n=10)	Total (N=35)	*P* value
Age, years (range)	74 (67–77)	70 (66–87)	74 (67–78)	0.99
Gender (male)	19 (76)	6 (60)	25 (71)	0.34
Creatinine µmol/L (range)	294 (186–386)	210 (188–312)	243 (187–385)	0.58
Estimated glomerular filtration rate (ml/min per 1.73 m^2)	19 (12–33)	24 (16–29)	20 (1–32)	0.58
New York Heart Association III/IV	16 (64)	7 (70)	23 (66)	0.74
Ischemic heart disease	14 (56)	7 (70)	21 (60)	0.45
Atrial fibrillation	14 (56)	6 (60)	20 (57)	0.83
Hyperlipidemia	22 (88)	6 (86)	28 (88)	0.87
Diabetes	16 (64)	7 (70)	23 (66)	0.74
Hypertension	16 (67)	10 (100)	26 (76)	0.04
Smoker	7 (29)	2 (29)	9 (29)	0.98
Pacemaker device	5 (20)	4 (40)	9 (26)	0.22
Implantable cardioverter defibrillator	1 (4)	2 (20)	3 (9)	0.13
Cardiac resynchronization therapy	3 (12)	1 (10)	4 (11)	0.87
Angiotensin converting enzyme inhibitor	11 (44)	1 (10)	12 (34)	0.1
Angiotensin receptor blocker	2 (8)	2 (20)	4 (11)	0.31
Beta blocker	21 (84)	9 (90)	30 (86)	0.13
Spironolactone	10 (40)	7 (70)	17 (49)	0.05
Furosemide	18 (72)	10 (100)	28 (80)	0.06
Metolazone	0 (0.0)	2 (20)	2 (6)	0.02
Hydrochlorothiazide	0 (0.0)	1 (10)	1 (3)	0.11
Anticoagulation	13 (52)	4 (40)	17 (49)	0.52
Daycare	22 (88)	7 (70)	29 (83)	0.2
Left ventricle ejection fraction				
> 50%	7 (32)	4 (40)	11 (34)	0.65
40–50%	4 (18)	3 (30)	7 (22)	0.45
< 40%	11 (50)	3 (30)	14 (44)	0.29
Right ventricle systolic function				
Mild	13 (57)	6 (60)	19 (58)	0.85
Moderate	7 (30)	1 (10)	8 (24)	0.21
Severe	2 (9)	3 (30)	5 (15)	0.12
Mitral regurgitation ≥ Moderate	15 (65)	7 (70)	22 (67)	0.79
Tricuspid regurgitation ≥ Moderate	18 (82)	9 (90)	27 (84)	0.55
Severe pulmonary hypertension	13 (54)	2 (33)	15 (50)	0.36
One-year mortality				
All	7 (28)	1 (10)	8 (23)	0.25
Sepsis	2 (8)	1 (10)	3 (9)	0.85
Heart failure	3 (12)	0 (0.0)	3 (9)	0.25
Overall mortality				
All	12 (50)	4 (50)	16 (50)	1
Sepsis	3 (13)	3 (38)	6 (19)	0.12
Heart failure	3 (13)	1 (13)	4 (13)	1

HD = hemodialysis; PD = peritoneal dialysis
Data are presented as median (interquartile range) for continuous variables and counts (percentages) for categorical variables
P value by the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables

Figure 1. HF hospitalizations one-year pre and post dialysis

Median HF hospitalizations during the year after dialysis was significantly reduced compared to the year prior to dialysis (0.0 [0.0–1.0] vs. 2.0 [0.0–3.0], $P < 0.001$

HF = heart failure



safe and reduced congestion, these studies did not reveal consistent results in terms of increased weight loss or improved kidney function compared to diuretics. Costanzo and colleagues [17] assessed the effect of ultrafiltration in patients with decompensated HF in the UNLOAD trial, in which it was found to be superior to intravenous diuretics in regard to weight and fluid loss as well as reducing hospitalizations. In the CUORE trial [19] ultrafiltration failed to reduce weight compared to pharmacological therapy; however, it did achieve its primary endpoint: reduction in rehospitalizations. In patients with worsening renal function, ultrafiltration was not superior in weight loss compared to pharmacologic-therapy, did not preserve renal function more, and was associated with higher adverse events [18].

Fluid removal by dialysis has been evaluated for the treatment of intractable volume overload in chronic HF and the results are more consistent. These studies have shown that dialysis improves clinical complaints of congestion, improves functional capacity, quality of life and reduces rehospitalization rates [4-10]. The present study demonstrates that the mainstay effect of dialysis therapy in our patients was a significant reduction of hospitalizations due to HF. Indeed, reduced number of hospitalizations is the main effect of dialysis in patients with HF [20]. Reduction in HF hospitalization is an important goal, as each decompensation episode is related to worsening of life expectancy [21].

In the present study, mortality rates were higher compared to the general end-stage renal disease (ESRD) population (87% 1-year survival; 50% 4-year survival, according to data from the Israel Center for Disease Control) [22]. However, this mortality rate is similar to what is described in similar cohorts of HF patients presenting with advanced disease [11]. Although dialysis reduces HF hospitalizations, it also brings an additional risk of complications. In our cohort, 17% of the deaths were attributed to line-related or peritoneal dialysis-related sepsis during follow-up, half during the first year after commencement of dialysis. Both types of dialysis modalities were affected, although numerically the rate was higher in the peritoneal dialysis (PD). This infection rate seems higher that reported in patients on dialysis: 0.03–0.14 admissions per patient-year for access related infections and 0.34–0.42 admissions per patient-year for all infections in ESRD Medicare beneficiaries [23]. Infections are obviously a significant risk with this invasive therapy and this situation needs to be considered in the individual patient, balancing the risk benefit ratio. Nevertheless, the mortality rate in the present study was not significantly different from the expected mortality in this severely compromised population.

Drug management in HF patients with chronic kidney disease is frequently limited by worsened kidney function and life-threatening hyperkalemia [9,24]. This result was seen in our cohort, in which most of the patients were less likely to receive full optimal medical treatment including ACE inhibitors/ARBs and mineralocorticoid receptor antagonists. Dialysis presents the opportunity to optimize the treatment and to increase medications. Whether it might improve the prognosis in this special patient cohort has to be demonstrated in further prospective studies.

LIMITATIONS

This retrospective observational study did not include a control group. The data included a relatively small number of patients from one specific hospital; therefore, the results may not be applicable to other populations. Patients performing dialysis receive meticulous care and intensified medical attention; thus, we cannot preclude that it is possible that intensification of medical care due to the dialysis may be the cause of the reduction in hospitalizations.

CONCLUSIONS

Dialysis significantly reduced HF hospitalization in advanced HF patients. Our study supports this option as a viable therapeutic option for intractable volume overload in advanced HF.

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References

1. Al-Omary MS, Khan AA, Davies AJ, et al. Outcomes following heart failure hospitalization in a regional Australian setting between 2005 and 2014. *ESC Heart Fail* 2018; 5 (2): 271-8.
2. Crespo-Leiro MG, Metra M, Lund LH, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018; 20 (11): 1505-35.
3. Neuberg GW, Miller AB, O'Connor CM, et al. Diuretic resistance predicts mortality in patients with advanced heart failure. *Am Heart J* 2002; 144 (1): 31-8.
4. Cnossen TT, Kooman JP, Krepel HP, et al. Prospective study on clinical effects of renal replacement therapy in treatment-resistant congestive heart failure. *Nephrol Dial Transplant* 2012; 27 (7): 2794-9.
5. Koch M, Haastert B, Kohnle M, et al. Peritoneal dialysis relieves clinical symptoms and is well tolerated in patients with refractory heart failure and chronic kidney disease. *Eur J Heart Fail* 2012; 14 (5): 530-9.
6. Núñez J, González M, Miñana G, et al. Continuous ambulatory peritoneal dialysis as a therapeutic alternative in patients with advanced congestive heart failure. *Eur J Heart Fail* 2012; 14 (5): 540-8.
7. Rizkallah J, Sood MM, Reslerova M, et al. Reduced hospitalizations in severe, refractory congestive heart failure with peritoneal dialysis: a consecutive case series. *Clin Nephrol* 2013; 80 (11): 334-41.
8. Bertoli SV, Musetti C, Ciurlino D, et al. Peritoneal ultrafiltration in refractory heart failure: a cohort study. *Perit Dial Int* 2014; 34 (1): 64-70.
9. Courivaud C, Kazory A, Crépin T, et al. Peritoneal dialysis reduces the number of hospitalization days in heart failure patients refractory to diuretics. *Perit Dial Int* 2014; 34 (1): 100-8.
10. Grossekettler L, Schmack B, Meyer K, et al. Peritoneal dialysis as therapeutic option in heart failure patients. ESC Heart Fail. 2019; 6 (2): 271-9.
11. Taylor CJ, Ordóñez-Mena JM, Roalfe AK, et al. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population based cohort study. *BMJ* 2019; 364: l223.
12. Rangaswami J, Bhalla V, Blair JEA, et al. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation* 2019; 139 (16): e840-78.
13. Damman K, Testani JM. The kidney in heart failure: an update. *Eur Heart J* 2015; 36 (23): 1437-44.
14. Khoury S, Steinvil A, Gal-Oz A, et al. Association between central venous pressure as assessed by echocardiography, left ventricular function and acute cardio-renal syndrome in patients with ST segment elevation myocardial infarction. *Clin Res Cardiol* 2018; 107 (10): 937-44.
15. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol* 2008; 52 (19): 1527-39.
16. Bart BA, Boyle A, Bank AJ, et al. Ultrafiltration versus usual care for hospitalized patients with heart failure. *J Am Coll Cardiol* 2005; 46 (11): 2043-6.
17. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol* 2005 2007; 49 (6): 675-83.
18. Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med* 2012; 367 (24): 2296-304.
19. Marenzi G, Muratori M, Cosentino ER, et al. Continuous ultrafiltration for congestive heart failure: the CUORE trial. *J Card Fail* 2014; 20 (1): 9-17.
20. Puttagunta H, Holt SG. Peritoneal dialysis for heart failure. *Perit Dial Int* 2015; 35 (6): 645-649.
21. Gheorghiade M, Vaduganathan M, Fonarow GC, Bonow RO. Rehospitalization for heart failure. *J Am Coll Cardiol* 2005 2013; 61 (4): 391-403.
22. Renal Replacement Therapy in Israel 1990-2015. Israel Ministry Society of Health and the Israel Society for Nephrology and Hypertension, ICDC Publication No 367. Jerusalem, Israel, 2018. [Available from: https: //www.health.gov.il/publicationsfiles/rrt1990_2015.pdf]. [Accessed 11 April 2021].
23. United States Renal Data System. 2020 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2020. [Available from: https: //adr.usrds.org/2020/end-stage-renal-disease/4-hospitalization]. [Accessed 11 April 2021].
24. Berger AK, Duval S, Manske C, et al. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with congestive heart failure and chronic kidney disease. *Am Heart J* 2007; 153 (6): 1064-73.

Capsule

Organized immunity in the oral mucosa

The oral cavity is the first site of contact with foodborne pathogens, yet how adaptive immune responses to antigens in the oral mucosa are regulated is not well understood. **Barreto de Albuquerque** and colleagues modeled foodborne listeriosis using oral *Listeria monocytogenes* (Lm) infection in mice. Lm drained from the oral mucosa to mandibular lymph nodes (mandLNs), resulting in local CD8+ T cell activation and effector (TEFF) generation. mandLN-primed TEFF disseminated to the lung, oral mucosa, and secondary lymph nodes to mount protective effector responses. The cells did not disseminate to the small intestine because of reduced expression levels of gut-homing receptors. Thus, priming of CD8+ T cells in mandLNs contributes to host protection, extending the concept of compartmentalized immune responses within the gastrointestinal tract.

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Capsule

Amyloid aids melanoma

Metastasis occurs when cancer spreads from the primary tumor throughout the body. Melanoma is a skin cancer that preferentially spreads to the brain, but what facilitates brain metastasis is not well understood. **Kleffman** and co-authors reported that the amyloid beta (Aβ) protein, which is a major contributor to neurodegeneration in patients with Alzheimer's disease, is required for melanoma growth in the brain parenchyma. Targeting amyloid precursor protein (APP) or APP cleavage products created an anti-inflammatory environment that allowed melanoma cells to avoid phagocytic clearance by microglia. Pharmacological inhibition of Aβ reduced melanoma metastasis.

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