A wearable hemofilter for continuous ambulatory ultrafiltration

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Ultrafiltration is effective for treating fluid overload, but there are no suitable machines for ambulatory treatment. This study summarizes the use of a light-weight wearable continuous ambulatory ultrafiltration device consisting of a hollow fiber hemofilter, a battery operated pulsatile pump, and two micropumps to control heparin administration and ultrafiltration. Six volume-overloaded patients underwent ultrafiltration for 6 h with treatment discontinued in one patient due to a clotted catheter. Blood flow averaged 116 ml min^{-1}, the ultrafiltration rate ranged from 120–288 ml h^{-1} with about 150 mmol of sodium removed. Blood pressure, pulse, and biochemical parameters remained stable with no significant hemolysis or complications. Our data show that the wearable hemofilter appears to be safe, effective, and practical for patients. This device could have a major impact on the quality of life of fluid-overloaded patients with heart failure. Additional studies will be needed to confirm these initial promising results.

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KEYWORDS: CRRT; ultrafiltration; fluid overload; congestive cardiac failure; wearable hemofiltration device

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The population affected by congestive heart failure (CHF) continues to expand due to the epidemic growth in the incidence of diabetes, obesity, coronary heart disease, and diastolic dysfunction.[1–3] The improved survival of patients with ischemic heart disease and myocardial infarction fuels further increments in this population. CHF New York Heart Association (NYHA) class III and IV patients are a very significant financial burden to US hospitals and the Medicare program.[4,5] CHF outcomes have improved somewhat with the advent of both pharmacological advances including; angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, natriuretic peptide analogues, diuretics, β-blockers, vasopressin receptor blockers, and also the use of pacemakers and implantable defibrillators.[6–8] However, despite these advances, the treatment of fluid overload and sodium retention, which are the hallmarks of decompensated CHF, remains problematical, and continues to cause morbidity and hospitalization. These two complications are exacerbated by neurohormonal disturbances and systemic inflammation.[9–11] In addition, aggressive diuretic administration may worsen renal function, and thus increasing mortality in these patients.[12,13] Peritoneal and hemodialysis have been advocated as useful treatments in severe cases of CHF refractory to diuretic therapy.[14,15] There is a growing body of scientific literature supporting the notion that the physical removal of fluid, cytokines and/or a myocardial depressant factor by convection[9] (that is, blood ultrafiltration) can significantly improve patient outcomes, and both shorten hospital inpatient stays and intensive care unit utilization.[16–22] However, current ultrafiltration methods require the use of stationary and bulky devices, reliant on mains electricity supply, which do not allow prolonged or continuous ultrafiltration. In addition, such acute hemofiltration treatments performed over 4–6 h, although efficient and capable of removing up to 23 l of ultrafiltrate in a single session[23] are not physiological, and can potentially result in major shifts of fluid from the intravascular compartment, leading to hypotension, and hemodynamic instability. Furthermore, they do not provide for a steady removal of excess fluid and sodium.

A small wearable device that allows ambulatory hemofiltration to be performed in a slow and continuous fashion

could afford patients the possibility of eliminating acute hemodynamic changes and the freedom from spending many hours attached to large stationary ultrafiltration machines currently used for continuous renal replacement therapies. This is not a new concept, as the first attempts to provide such continuous treatments, date back more than 30 years ago, to the pioneering reports by Kolff.[24] We have previously described the feasibility, safety, and efficacy of the wearable artificial kidney (WAK),[25] as well as its use as an ultrafiltration device, in animal studies.[26] This device might not only potentially contribute to improve the quality of life and reduce the mortality of the ever-growing CHF population, but also make these therapies more affordable and reduce the financial burden incurred in treating this condition. This study describes the first human use of a wearable hemofiltration device (Figure 1) to manage fluid overload. As such, this was a preliminary study, designed as proof of concept, and also to assess both patient tolerability and safety.

RESULTS

Six patients with fluid overload successfully underwent hemofiltration using a wearable ultrafiltration device. Patient and treatment parameters are outlined in Tables 1–4. The hourly amount of ultrafiltration fluid removed ranged from 120 to 288 ml h^{-1}. The amount of ultrafiltrate was measured both by volume and weight and corresponded to the rate of removal indicated by the pump. The average ultrafiltration rate was 192 ± 68.3 ml h^{-1}, with a mean total ultrafiltrate volume of 1084.33 ± 335 ml. The average blood flow was 116 ± 11 ml min^{-1}. Patient weights fell from 77.7 to 76.2 kg, despite patients being encouraged to eat and drink.

The total amount of sodium removed was 150.7 ± 46.5 mmol. The pretreatment serum sodium was 137.3 ± 3.1 mmol l^{-1}, and did not significantly change during treatment, being 138 ± 4.0 mmol l^{-1} after 3 h and 139 ± 3.6 mmol l^{-1} after 6 h of treatment. Similarly, the pretreatment serum potassium was 5.1 ± 1.0 mmol l^{-1} and did not change, being 5.1 ± 0.9 mmol l^{-1} at the end of the study. The sieving coefficients for creatinine and urea were 0.98 ± 0.02 and 0.96 ± 0.05, respectively. The mean urea and creatinine clearances were 3.1 ± 0.9 and 3.2 ± 1.0 ml min^{-1}, respectively.

There were no significant changes in heart rate, respiratory rate, and/or temperature during the 6 h of ultrafiltration treatment. There was a marginal, but significant decrease in mean arterial pressure from 109.4 ± 18.5 to 101.8 ± 17.3 mm Hg ($P < 0.03$) (Table 3).

There were no changes in ECG pre- and posttreatment with the hemofiltration device, and no observed arrhythmias or changes in oxygen saturation. As fluid was successfully removed, the hematocrit did increase after both 3 and 6 h of treatment (Table 4). There was a modest but significant fall in the peripheral platelet count. As with the hematocrit, there was a marginal increase in serum lactate dehydrogenase. This was probably due to a plasma volume effect rather than significant hemolysis.

Initially, all patients were treated when lying down on a bed, but during the study, all patients that so desired got out of bed and walked around (Figure 2). There were no technical complications or untoward effects, in terms of blood pump malfunction, disconnections, and/or ultrafiltration/heparin pump errors. However, in one patient treatment had to be terminated after 4 h due to a clotted catheter. All patients were favorably impressed with the treatment, and no patient made any complaints. During the study, patients were encouraged to be ambulatory, eat and drink, so as to try and simulate ordinary daily activity, while being connected to the wearable hemofiltration device.

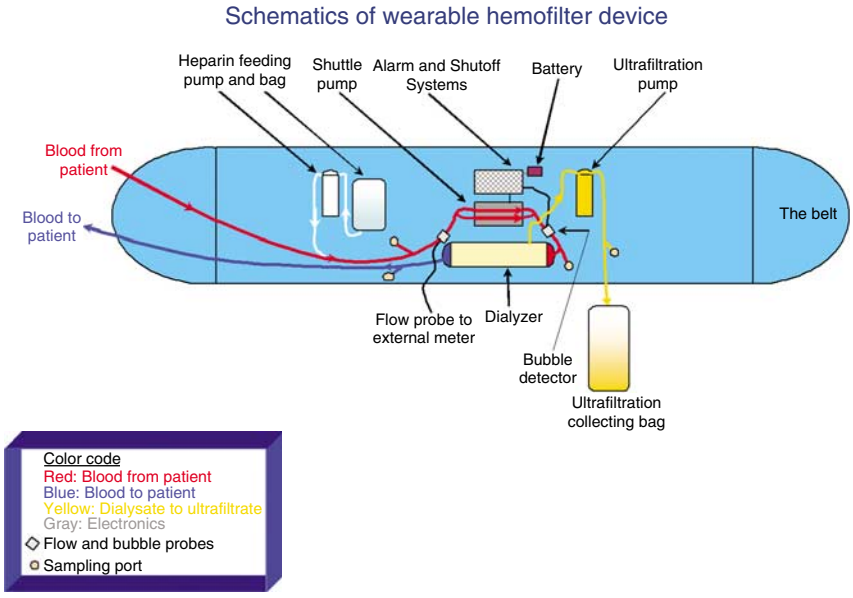

Figure 1 | Diagram of the wearable hemofilter.

DISCUSSION

Although the wearable hemofiltration device was designed as a potential treatment for patients with refractory cardiac failure, NYHA class IV, as this was the first-ever human study, we elected to choose established hemodialysis patients, for this proof of concept pilot trial. Established hemodialysis patients were chosen, as they had already had established central venous access catheters, used unfractionated heparin for their routine hemodialysis treatments, and were volume overloaded, as referenced to their known postdialysis target weight.

In this initial proof of concept pilot study, six fluid-overloaded patients underwent ambulatory hemofiltration safely and effectively. Patients were encouraged to walk around, eat, and perform some of the tasks of daily living to assess the portability and comfort of the device. This first-ever human study of a wearable artificial hemofiltration device indicates that its application as such is feasible. The preliminary data on the safety of the wearable hemofiltration device is that the six patients showed no symptoms or signs of complications. Blood pressure and heart rate did not significantly change during hemofiltration. As expected, during ultrafiltration, the hematocrit increased marginally, although significantly. There was a minor but significant change in peripheral platelet count. Although the serum lactate dehydrogenase levels did increase slightly, this was most likely, due to the reduction in plasma water, rather than any significant hemolysis during treatment.

As this was a hemofiltration device, primarily designed to treat patients with refractory heart failure, the amounts of urea and creatinine removed were less than that during comparable dialysis.

The preliminary data supporting the efficacy of the wearable hemofiltration device showed that the volumetrically controlled ultrafiltrate removal was accurate, according to the amounts programmed into the built in control system, over a wide range of volumes, from 120 to 288 ml h^{-1} with an accuracy of $\pm 6\%$. There were no operational difficulties or technical complications during the study, thus confirming the results we obtained in previous animal studies.[25,26]

The wearable hemofiltration device was shown in this proof of concept study to be an effective tool for the removal of excess sodium. A total 150.7 ± 46.5 mmol of sodium was removed during this pilot study. If this was to be scaled up to 24 h sodium loss, this would equate to approximately 634 mmol (which is equivalent to 37 g of sodium chloride). Patients with refractory cardiac failure are encouraged to eat a low-sodium diet, typically restricting dietary salt intake to 2 or 3 g day^{-1}. This sodium loss is much greater than urinary sodium losses that were achieved by simple loop diuretics, and could potentially allow patients to have a less restricted diet, with improvement in both terms of intake of food and quality of life.

As this wearable device was designed as a hemofilter, the absolute removal of urea and creatinine were much less than that during a standard hemodialysis treatment. It may be possible to add a dialysate component to the circuit to

Table 1 | Patient characteristics

Patient no.	Sex	Age	Etiology of kidney disease	Months on dialysis
1	Male	50	Hypertension	6
2	Male	68	Diabetes	1
3	Male	68	Glomerulonephritis	108
4	Female	41	Polycystic kidneys	29
5	Male	42	Polycystic kidneys	2
6	Male	84.6	Hypertension and diabetes	20

Table 2 | Treatment characteristics of the wearable hemofiltration device

Patient no.	Qb (ml min^{-1})	Q_{UF} (ml h^{-1})	Heparin (IU h^{-1})	Rx time (h)	Final aPTT (s)	SC urea	SC creatinine
1	134.2	120	758.3	6	107	1.00	0.97
2	118.9	288	300	4	49	0.96	0.98
3	121.9	120	1000	6	150	0.93	0.96
4	106.1	250	500	6	60	0.88	0.96
5	106.8	175	533.3	6	72	1.00	1.01
6	108.6	200	1000	6	137	1.00	1.01
Mean	116.1	192.1	681.9	5.7	95.8	0.96	0.98
s.d.	11.1	68.3	286.1	0.8	41.9	0.05	0.02

Shows blood flow (Qb), ultrafiltration rate (Q_{UF}), duration of treatment (Rx time), activated partial thromboplastin time (aPTT), and sieving coefficients (SCs) for urea and creatinine.

Table 3 | Patient parameters during treatment with the wearable hemofiltration device

Patient no.	1	2	3	4	5	6	Mean ± s.d.	*P*-value
MAP mm Hg pre-UF	119.0	111.0	90.3	88.3	138.0	109.7	109.4 ± 18.5	
MAP mm Hg post-UF	87.3	111.0	98.7	76.7	120.0	117.0	101.8 ± 17.3	0.03
Total UF (ml)	770	984	708	1610	1233	1201	1084.3 ± 335.4	
Na_{UF} (mmol)	107.8	132.8	97.0	223.8	172.6	171.7	150.0 ± 47.6	

Shows mean arterial pressure (MAP), volume ultrafiltered (UF), and sodium removed in ultrafiltrate (Na_{UF}). Data expressed as mean ± s.d.

Table 4 | Patient hematocrit (Hct), peripheral platelet count, and lactate dehydrogenase (LDH)

Patient no.	Hct (%)			Platelet (10^9 l^{-1})			LDH (U l^{-1})		
	0 h	3 h	6 h	0 h	3 h	6 h	0 h	3 h	6 h
1	38.9	39.6	39.1	221	197	212	427	458	457
2	23.1	23.5	23.1	235	203	227	658	680	670
3	31.2	31.6	32.8	147	110	105	198	261	271
4	32.9	34.2	34.3	105	110	107	220	279	309
5	41.1	42.1	43.1	210	197	177	348	413	470
6	28.7	31.7	31.0	236	249	237	350	415	407
Mean	32.65	33.8	33.9	192.3	177.7	177.5	366.8	417.7	430.7
s.d.	6.6	6.6	6.9	53.9	55.9	59	166.8	151.2	141.7
P-value	0.031	0.031	0.031	0.031	0.035	0.031	0.031	0.031	0.031

Figure 2 | A patient ambulating while undergoing treatment with the wearable hemofilter.

improve solute clearances, but this would require a sorbent system to adsorb solutes.[25] Other workers are similarly trying to develop a wearable dialysis device that does not require any additional dialysate using nanotechnology.[27]

The wearable hemofiltration device requires extracorporeal anticoagulation. For this initial proof of concept trial, unfractionated heparin was chosen, as the participants were regularly heparinized for their routine hemodialysis treatments. As such, the heparin dose used for each patient was empirically based on their previous hemodialysis treatments. No patient suffered bleeding, although one patient had the treatment terminated after 4 h due to catheter clotting, as the activated partial thromboplastin time had fallen toward its normal range. Further trials are required to determine heparin requirements for extended treatments, and potentially other anticoagulants might be used.

For this proof of concept initial trial, the wearable hemofiltration device was assembled on a belt worn around the abdomen. The proposed blood access for standard future application during prolonged treatment would be a double-lumen central venous catheter, tunneled under the skin, and exiting at the level of the waist. Double cuffs would be placed on the catheter to generate a mechanical barrier to potential tunnel infection. Although we would prefer the vascular access described above, other types of access may be used by treating nephrologists, as experience with the wearable hemofiltration device accumulates.

There is a growing body of literature supporting the concept that blood ultrafiltration is an effective therapy for the treatment of refractory fluid-overloaded patients with CHF, and other hypervolemic states.[16–22] In addition, ultrafiltration has been shown to improve cardiac function without deterioration of renal function in CHF patients, in contrast to the deleterious effects of diuretics on glomerular filtration rate,[12,13,28,29] and in some cases, renal function actually may be improved.[30] Changes in serum creatinine from <2 to >2 mg per 100 ml, in patients with CHF, have been recently associated with a doubling in mortality.[31,32] Thus, a significant reduction in the use of diuretics, which is known to decrease the glomerular filtration rate and increase serum creatinine, would hopefully be beneficial in preventing worsening azotemia resulting from massive diuretic use, and hopefully, reduce mortality. Ultrafiltration has been shown to have significant beneficial effects in the electrolyte and neurohormonal derangements associated with refractory heart failure[33] and allows for the avoidance of excessive and ineffective diuretic treatment that is so often conducive to renal failure, hypotension, and further metabolic complications. This contention is supported by the UNLOAD trial, which has recently reported that ultrafiltration safely produced greater weight and fluid loss than intravenous diuretics, and in addition, reduced the 90-day health-care resource utilization and treatment costs for patients with decompensated heart failure.[34]

Until now, ultrafiltration could only be accomplished with stationary dialysis machines or ultrafiltration devices that are not amenable to be worn on the patient's body and used continuously while the patient is ambulatory. To our knowledge, there is no other device available in the therapeutic arsenal to potentially treat ambulatory patients with continuous ultrafiltration. In comparing the wearable hemofiltration device to those machines currently used for hemofiltration, the WAK weights less than 2.5 pounds (1.135 kg), requires a standard 9-V battery and adapts ergonomically to the body contour, allowing wearability,

with minimal interference to the activities of daily life. In contrast, currently used machines are heavy, require a mains electrical power source, and cannot be worn on the body, thus impeding the ability of the patient to move around and conduct activities of daily life while undergoing treatment. Current machines, allow only for the removal of large, unphysiological amounts of fluid in relatively short periods. This, in turn, can lead to adverse hemodynamic changes. Although the wearable hemofiltration device is unlikely to cause this, as the rate of fluid removal is of similar magnitude to urine output, and the blood flow necessary to achieve these results of approximately 50–120 ml min is lower than that of most commonly used hemofiltration and/or dialysis machines. The fundamental characteristics of the device are the lightweight, small size, and wearability.

The clinical significance of the wearable hemofiltration device is the potential to reduce the incidence of acute pulmonary edema, ascites, and other stigmata in patients with NYH class III and IV CHF. Hopefully, further development of this technique will lead to the introduction of this therapy for patients with diuretic refractory heart failure, and reduction in both morbidity and mortality. If further clinical trials confirm the effectiveness and safety of this device, then the economic impact in terms of the reduction in length of hospital stay, ICU utilization and drug consumption, as well as the number of hospital admissions could potentially be considerable.

MATERIALS AND METHODS

The study was conducted at Ospedale San Bortolo, Vicenza, Italy after approval by the Internal Bioethical Committee as provided in the Declaration of Helsinki Principles.

As this was the first use in humans, and a proof of concept study, patients with chronic kidney disease established on regular hemodialysis, using a central venous dual lumen access catheter for blood access, were recruited. These patients were chosen rather than those with CHF, as they already had established venous access and were regularly given heparin for extracorporeal anticoagulation. Six patients volunteered for the study (Table 1). At the time of the study, all patients were above their regular dry weight determined for dialysis, the degree of fluid overload, ranging from 0.7 to 4.3 kg.

After obtaining appropriate informed consent, the venous access catheter was connected to the wearable hemofiltration device, and hemofiltration was performed in six patients. Five patients were treated for 6 h and one patient was treated for only 4 h when treatment had to be discontinued due to a clotted catheter. The wearable artificial hemofiltration device (Xcorporeal Inc., Los Angeles, CA, USA) comprised a standard commercially available high flux hemofilter (Medica, Medolla, Italy), made of polysulfone (inner diameter 250 microns, 2500 hollow fibers, 0.25 m^2). A specially designed pulsatile blood pump, that used a standard 9-V battery as the energy source, and 2 micropumps (Sorenson, West Jordan, UT, USA), one for heparin administration and another to control the amount of ultrafiltrate removed (Figure 1). The total weight of the device was 2.5 lb (1.135 kg).

The amount of unfractionated heparin infused ranged from 300 to 1000 IU h^{-1}, (Table 2) and was based on the usual amount of heparin administered during their routine hemodialysis, then adjusted according to activated partial thromboplastin time.

The safety features of this wearable device included a servomechanism with a bubble detector sensor placed after the blood pump, designed to stop blood flow if air bubbles were detected in the blood circuit, a second servomechanism that would halt the ultrafiltration pump if the blood flow stopped for any reason. In addition, the pulsatile blood pump had a self-limited capacity to generate negative pressure for suction from the arterial side of the catheter such that significant negative pressures could not be applied to the vascular access. Similarly, on the venous side of the circuit, any increased venous resistance would lead to cessation of the blood pump. In the event of clotting within the circuit, the changes in pressure would cause the blood pump to stop.

Blood flow was independently measured using an external separate flow meter (Transonic Systems, Ithaca, NY, USA). At the end of the treatment, all blood was returned to the patient and the device disconnected. During the ultrafiltration treatment, pulse, respiratory rate, blood pressure, and temperature were recorded at regular intervals. In addition, electrocardiograms were recorded pre- and posttreatment, and during the study, patients were monitored with pulse oximetry and cardiac monitoring (Accutorr plus; Datascope GmbH, Bensheim, Germany). The ultrafiltration rate for each individual patient was determined, after both clinical assessment of the degree of hypervolemia, and comparing pre-ultrafiltration weight with the known postdialysis target weight. Blood samples were taken from a sampling port in the blood tubing of the device and corresponding ultrafiltrate samples obtained as ultrafiltrate exited the filter at the beginning, after 3 h, and then at the end of the treatment. During treatment patients were encouraged to have lunch, drink fluids freely, and ambulate at their leisure.

Statistical analysis

Data were analyzed using Prism software (GraphPad, San Diego, CA, USA). The Wilcoxon signed-rank test was performed, and $P<0.05$ was considered significant.

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REFERENCES

1. Lewis CE, Jacobs Jr DR, McCreath H *et al.* Weight gain continues in the 1990s: 10-year trends in weight and overweight from the CARDIA Study. Coronary Artery Risk Development in Young Adults. *Am J Epidemiol* 2000; **151**: 1172–1181.
2. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. *Circulation* 2002; **105**: 1387–1393.
3. Gottdiener JS, McClelland RL, Marshall R *et al.* Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. The Cardiovascular Health Study. *Ann Intern Med* 2002; **137**: 631–639.
4. American Heart Association. *Heart Disease and Stroke Statistics—2007 Update*.
5. Krumholz HM, Parent EM, Tu N *et al.* Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. *Arch Intern Med* 1997; **157**: 99–104.
6. Stevenson LW. Tailored therapy to hemodynamic goals for advanced heart failure. *Eur J Heart Fail* 1999; **1**: 251–257.
7. Nohria A, Lewis E, Stevenson LW. Medical management of advanced heart failure. *JAMA* 2002; **287**: 628–640.
8. Fonarow GC. Pharmacologic therapies for acutely decompensated heart failure. *Rev Cardiovasc Med* 2002; **3**(Suppl 4): S18–S27.

9. Blake P, Hasegawa Y, Khosla MC *et al.* Isolation of 'myocardial depressant factor(s)' from the ultrafiltrate of heart failure patients with acute renal failure. *ASAIO J* 1996; **42**: M911–M915.
10. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. *N Engl J Med* 1999; **341**: 577–585.
11. Levine B, Kalman J, Mayer L *et al.* Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N Engl J Med* 1990; **323**: 236–241.
12. Brater DC. Diuretic therapy. *N Engl J Med* 1998; **339**: 387–395.
13. Neuberg GW, Miller AB, O'Connor CM *et al.* Diuretic resistance predicts mortality in patients with advanced heart failure. *Am Heart J* 2002; **144**: 31–38.
14. Cairns KB, Porter GA, Kloster FE *et al.* Clinical and hemodynamic results of peritoneal dialysis for severe cardiac failure with chronic edema. *Am Heart J* 1968; **76**: 227–234.
15. Hampl H, Paeprer H, Unger V *et al.* Hemodynamic changes during hemodialysis sequential ultrafiltration and hemofiltration. *Kidney Int* 1980; **18**: S83–S88.
16. Silverstein ME, Ford CA, Lysaght MJ *et al.* Treatment of severe fluid overload by ultrafiltration. *N Engl J Med* 1974; **291**: 747–751.
17. Kramer P, Wigger W, Rieger J *et al.* Arteriovenous haemofiltration: a new and simple method for treatment of over-hydrated patients resistant to diuretics (in German). *Klin Wochenschr* 1977; **55**: 1121–1122.
18. Donato L, Biagini A, Contini C *et al.* Treatment of end-stage congestive heart failure by extracorporeal ultrafiltration. *Am J Cardiol* 1987; **59**: 379–380.
19. Blake P, Paganini EP. Refractory congestive heart failure, overview and application of extracorporeal ultrafiltration. *Adv Ren Replace Ther* 1996; **3**: 166–173.
20. Ronco C, Ricci Z, Bellomo R, Bedogni F. Extracorporeal ultrafiltration for the treatment of over hydration and congestive heart failure. *Cardiology* 2002; **96**: 155–168.
21. Sheppard R, Panyon J, Pohwani AL *et al.* Intermittent outpatient ultrafiltration for the treatment of severe refractory congestive heart failure. *J Card Fail* 2004; **10**: 380–383.
22. Clark WR, Paganini E, Weinstein D *et al.* Extracorporeal ultrafiltration for acute exacerbations of chronic heart failure: report from the Acute Dialysis Quality Initiative. *Int J Artif Organs* 2005; **28**: 466–476.
23. Simpson IA, Rae AP, Simpson K *et al.* Ultrafiltration in the management of refractory congestive heart failure. *Br Heart J* 1986; **55**: 344–347.
24. Stephens RL, Jacobsen SC, Atkin-Thor E, Kolff W. Portable/wearable artificial kidney (WAK)—initial evaluation. *Proc Eur Dial Transplant Assoc* 1976; **12**: 511–518.
25. Gura V, Beizai M, Ezon C, Polaschegg HD. Continuous renal replacement therapy for end-stage renal disease: the wearable artificial kidney (WAK). *Contrib Nephrol* 2005; **149**: 325–333.
26. Gura V, Beizai M, Ezon C, Rambod E. Continuous renal replacement therapy for congestive heart failure: the wearable continuous ultrafiltration system. *ASAIO J* 2006; **52**: 59–61.
27. Nissenson AR, Ronco C, Pergamit G *et al.* Continuously functioning artificial nephron system: the promise of nanotechnology. *Hemodial Int* 2005; **9**: 210–217.
28. Francis GS, Siegel RM, Goldsmith SR *et al.* Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure: activation of the neurohumoral axis. *Ann Intern Med* 1985; **103**: 1–6.
29. Agostoni P, Marenzi G, Lauri G *et al.* Sustained improvement in functional capacity after removal of body fluid with isolated ultrafiltration in chronic cardiac insufficiency: failure of furosemide to provide the same result. *Am J Med* 1994; **96**: 191–199.
30. Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. *Am Heart J* 1999; **138**: 285–290.
31. Hillege HL, Girbes ARJ, de Kam PJ *et al.* Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation* 2000; **102**: 203–210.
32. ADHERE Registry. Acute Decompensated Heart Failure National Registry. Q1 2004 National Benchmark Report. Adair-Greene Healthcare Communications: Atlanta, GA, 2004, pp 1–21.
33. Guazzi MD, Agostoni P, Perego B *et al.* Apparent paradox of neurohumoral axis inhibition after fluid volume depletion in patients with chronic congestive heart failure and water retention. *Br Heart J* 1994; **72**: 534–539.
34. Costanzo MR, Guglin ME, Saltzberg MT, *et al.*, UNLOAD Trial Investigators. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol* 2007; **49**: 675–683.