Ultrafiltration: contemporary management of fluid overload

Introduction

Chronic heart failure is common, with an incidence of 1 in 1000 of the general population, and is rising at 10% per year (Cowie et al, 1999; Owan et al, 2006). In the UK, the prevalence is estimated at 900 000 patients, with only 7000 of these under the age of 65 years (Petersen et al, 2002). Approximately 200 000 are in New York Heart Association (NYHA) functional class III/IV, meaning they are breathless on mild exertion.

Currently this population is responsible for 1 000 000 inpatient bed days, and this figure is expected to increase by 50% over the next 25 years (Stewart and Horowitz, 2002; Stewart et al, 2002). Five per cent of all emergency admissions in the UK are the result of heart failure. Heart failure represents 1.8% of the total NHS budget (currently £110 billion), and of this figure 70% is related to hospital admissions. Readmission rates are high and are predominantly the result of fluid accumulation which impacts upon disease progression and is associated with increased mortality.

Fluid overload occurs as a result of pump failure and the resulting decrease in cardiac output and renal perfusion causing activation of the sympathetic and renin–angiotensin–aldosterone systems, which causes salt and water retention, increasing myocardial work and worsening pump failure. This review details the reasons that alternative therapies for fluid overload are needed, and presents the evidence for the use of ultrafiltration in the contemporary management of advanced heart failure.

Diuretic therapy in heart failure

The first-line treatment for congestion in patients with heart failure is diuretics which, despite a lack of safety and efficacy from randomized controlled trials, have had decades of proven clinical utility. Pharmacological treatment of left ventricular systolic impairment with angiotensin-converting enzyme inhibitors, beta blockers and mineralocorticoid receptor antagonists all have class 1, level of evidence A recommendations in current European Society of Cardiology guidelines (McMurray et al, 2012).

The relative risk reduction of death or heart failure hospitalization is 16–27% for angiotensin-converting enzyme inhibitors (CONSENSUS, 1987; SOLVD, 1991; Garg and Yusuf, 1995), an additional 28–36% for beta blockers (in patients already on angio-tensin-converting enzyme inhibitors) (CIBIS-II, 1999; MERIT-HF, 1999; Packer et al, 2001, 2002) and 30–37% for mineralocorticoid receptor antagonists (Pitt et al, 1999; Zannad et al, 2011).

Despite a wealth of evidence for long-term prognostic drugs in heart failure, treatment options for fluid overload are limited: a low sodium diet, fluid restriction and diuretics. Dietary and fluid measures may be less important in acute (Aliti et al, 2013) compared with chronic (Arcand et al, 2011) heart failure, although are still supported by current guidelines (McMurray et al, 2012).

Although loop diuretics cause fluid loss and symptom resolution, repeated exposure is associated with reduced effect and can be associated with increased morbidity and mortality as a result of deleterious effects on neurohormonal activation, electrolyte balance, cardiac and renal function.

Diuretic resistance has been described as a clinical state in which the diuretic response is diminished or lost before the therapeutic goal of relief from oedema has been reached. In up to 30% of patients with diuretic resistance, this may be mediated by the 'braking' phenomenon (Kramer et al, 1999). This is poorly understood but is thought to be mediated by the renin–angiotensin–aldosterone system or sympathetic nervous system resulting in chronic sodium retention (Brater, 1998, Ellison, 2001). However, even when both of these pathways are blocked, the braking phenomenon still occurs.

Long-term diuretic tolerance is manifested by distal tubular hypertrophy, which occurs when increased amounts of solute arrive at that portion of the tubule (Kaissling and Stanton, 1988; Stanton and Kaissling, 1988; Kaissling and Loffing, 1998). The exact mechanism is not known. This type of resistance is a reason why combination diuretic therapy is often used, for example loop and distal diuretic simultaneously to maximize diuresis.

Patients with heart failure are relatively diuretic resistant and excrete less sodium compared to normal individuals for a given plasma concentration of furosemide (Ellison, 2001). In addition, the natriuretic threshold is increased, meaning that an oral dose of furosemide may not provide a high enough serum level to elicit natriuresis (Ellison, 2001). The timing of intravenous drug delivery is also important, as sodium excretion tails off relatively quickly after an intravenous bolus (Rudy et al, 1991). The DOSE study showed no difference in symptom reduction between bolus or continuous infusion of diuretics in decompensated heart failure (Felker et al, 2011).

Advanced heart failure therapy

Patients with fluid overload or symptoms unresponsive to basic heart failure therapy should be considered for advanced strategies. European guidelines offer a comprehensive strategy for the management of both acute and chronic heart failure (McMurray et al, 2012). In terms of medical management, this will often comprise positive inotropic support, often in a high dependency setting. Newer potential therapies include vasopressin antagonists, which treat fluid overload without many of the deleterious effects on renal function and electrolytes seen with diuretics. They have been proven to be safe, and well tolerated in phase II studies but are not yet in widespread use (Udelson et al, 2011; Ghali et al, 2012).

Patients fulfilling current criteria (Vardas et al, 2007) should be considered for car-

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diac resynchronization therapy. In general this applies to patients with heart failure and breathlessness. In patients with moderate to severe systolic dysfunction on optimal medical therapy the relative risk reduction of death is 24–36% (Bristow et al, 2004; Cleland et al, 2005), and of hospitalization for heart failure is 52% (Cleland et al, 2005). Similar reductions in the composite end point have been shown in mild–moderately symptomatic patients (Moss et al, 2009; Tang et al, 2010). However, while often successful in improving left-sided heart failure, cardiac resynchronization therapy may not effectively improve peripheral oedema.

Circulatory support, including ventricular assist device and extra-corporeal membrane oxygenation, is an important strategy in advanced heart failure management, but its use is generally restricted to cardiac transplant centres in bridge-to-transplant situations. As a result, availability is extremely limited. There is increasing evidence for ventricular assist device insertion as destination therapy (Rose et al, 2001; Dickstein et al, 2010), although this is currently not funded in the UK. Cardiac transplantation remains the gold standard of treatment for many end-stage heart failure syndromes, although organ availability and lack of intensive care beds mean this is not a viable option for the vast majority of patients (Macgowan et al, 2011).

Ultrafiltration

History

The concept of mechanical removal of fluid from patients with cardiac disease has been around for decades (Schneierson, 1949; Kolff and Leonards, 1954). In the early 1990s ultrafiltration was shown to be effective with results sustained up to 3 months, and benefits over those of diuretic administration (Agostoni et al, 1994). Food and Drug Administration approval for ultrafiltration was granted in 2002. Initial experience was with central venous cannulation, and the progression to peripheral use was proven clinically safe in 2003 (Jaski et al, 2003). Further clinical experience to establish guidelines for the use of ultrafiltration were published shortly thereafter (Bart et al, 2005; Costanzo et al, 2005).

European Society of Cardiology (McMurray et al, 2012), American Heart Association/American College of Cardiology (Hunt et al, 2009) and the Heart Failure Society of America (Lindenfeld et al, 2010) guidelines all now rate ultrafiltration as class IIa, level of evidence B, stating:

> **'Ultrafiltration should be considered to reduce fluid overload (pulmonary and/or peripheral oedema) in selected acute heart failure patients and correct hyponatremia in symptomatic patients refractory to diuretics' (McMurray et al, 2012).**

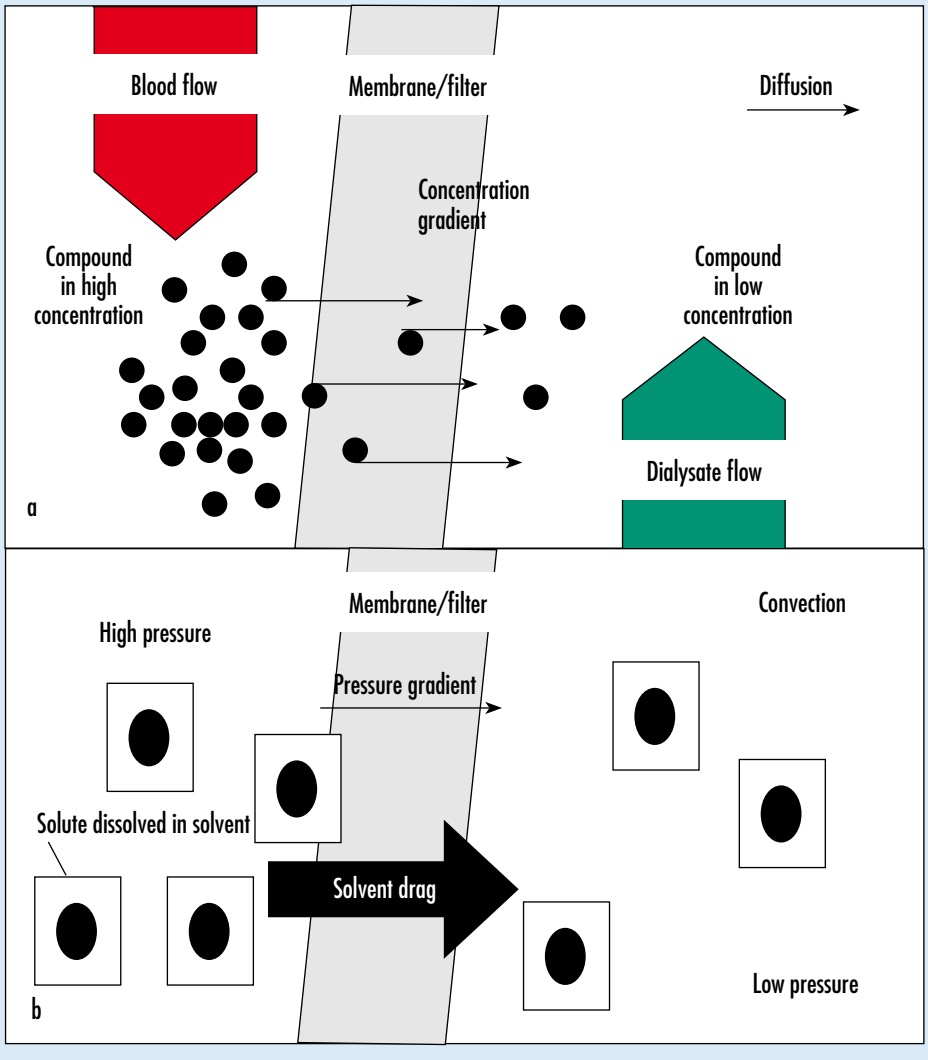
To date 50 000 patients have been treated worldwide.

Mechanism of action

Ultrafiltration works by using hydrostatic pressure to force blood against a semipermeable membrane. The resultant pressure gradient drives water and low molecular weight solutes through the membrane while cells and solutes of high molecular weight (e.g. blood cells, albumin, fibrin and platelets) are retained on the blood pool side and returned to the patient.

The major differences between ultrafiltration and dialysis are illustrated in *Figure 1*. Compared to medical therapy, ultrafiltration has a key advantage of maintaining complete control over the rate and total volume of fluid removed. Because isotonic fluid (with a high sodium content per unit) is removed, neurohormonal activation following treatment is reset toward a more physiological state and diuretic efficacy is restored (Marenzi et al, 2001).

Figure 1. Dialysis vs ultrafiltration: differences in mechanism of action. Both techniques involve the movement of blood and fluid separated on either side of a semi-permeable membrane. a. With dialysis solutes move along an electrochemical concentration gradient across the membrane, into dialysate which is actively pumped in the opposite direction to blood flow. b. In contrast, ultrafiltration removes dissolved solute which moves across a hydrostatic pressure gradient.



Therapy is not associated with electrolyte depletion (Jaski et al, 2003; Bart et al, 2005; Costanzo et al, 2007). An early invasive haemodynamic study in 24 patients with refractory heart failure treated with ultrafiltration showed immediate and progressive reduction in mean right atrial, pulmonary artery and wedge pressure and a subsequent rise in cardiac output and stroke volume, without an increase in heart rate, systemic vascular resistance or peripheral biochemical markers (Marenzi et al, 2001). Intravascular volume remained stable, suggesting the fluid removed in the circuit was being replaced by that from the overloaded tissues.

An example of an ultrafiltration machine and schematic of the component setup is shown in *Figures 2* and *3*. Before being attached to the patient, the circuit and filter are flushed with saline, and the patient is systemically heparinized to protect the circuit from clotting. The rate of blood flow and ultrafiltration is set, and the filter started. The circuit is limited by the manufacturer to 72 hours use. Ultrafiltration rate can be set from 50 to 500 ml/hour, but patients in volume-sensitive states (e.g. right heart failure, pulmonary distress, hepatic disease, cardiogenic shock) usually require lower rates (e.g. 50–150 ml/hour). Modern devices include haematocrit sensors, which estimate blood volume so that the rate can be adjusted to prevent hypovolaemia. The removal goal is often set to approximately 80% of the estimated weight over dry weight. For example, if a patient is estimated to be 10 kg above dry weight, the removal goal would be approximately 8 litres.

Figure 2. Aquadex flexflow ultrafiltration console.

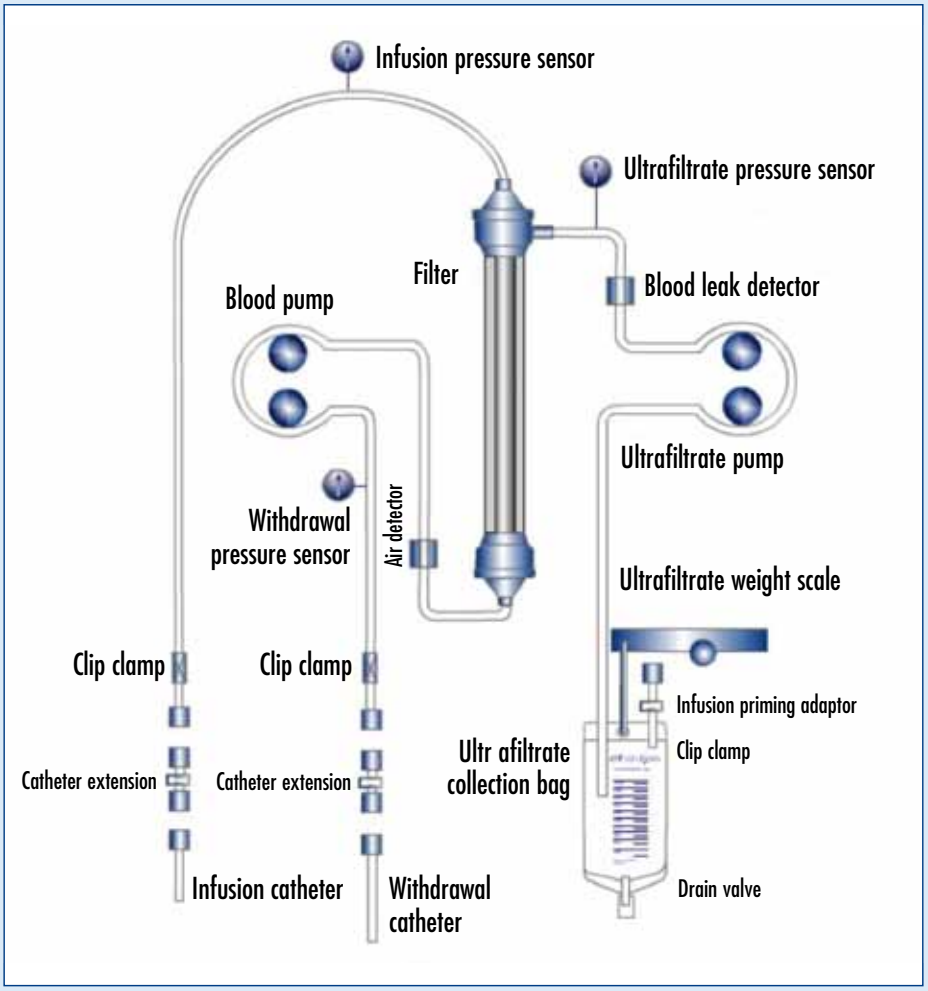
Clinical efficacy

Superiority over diuretic medication was demonstrated in 200 patients with decompensated heart failure randomly assigned to ultrafiltration or intravenous diuretic therapy (UNLOAD trial; Costanzo et al, 2007). Ultrafiltration safely produces greater weight and fluid loss than intravenous diuretics, fewer days in hospital if readmission is necessary, fewer emergency and unscheduled outpatient visits, and is an effective alternative therapy (Costanzo et al, 2007; Peterangelo, 2008). Use of ultrafiltration in UNLOAD was associated with a 53% reduction in the risk of rehospitalization for heart failure (hazard ratio 0.5625, 95% confidence interval 0.2848–0.5086, *P*=0.0367) without significant adverse events. Mean baseline creatinine was 133 µmol/litre in both groups, with no significant difference between groups during treatment and up to 90 days after treatment.

Standard intravenous diuretic therapy for peripheral oedema typically removes approximately 1 litre/day, significantly less than may be achieved with ultrafiltration. These factors combined offer the potential for financial savings for a patient population in whom hospital admission costs are significant. In addition to clinical outcomes, ultrafiltration has positive effects on haemodynamic indices and neurohormonal markers indicating the overall performance of the cardiovascular system, such as aldosterone and NT-pro BNP (Giglioli et al, 2011).

However, clinical outcomes in patients with decompensated cardio-renal syn-

Figure 3. Schematic representation of the components used to perform ultrafiltration.



dromes remain poor, and the role of ultrafiltration in this complex subset of patients remains uncertain. A randomized trial (Cardiorenal Rescue Study in Acute Decompensated Heart Failure, CARRESS-HF) comparing ultrafiltration with an aggressive drug regimen including diuretics and vasoactive agents in 188 patients with acute cardio-renal syndrome (baseline creatinine in the ultrafiltration group was 168 µmol/litre) and persistent congestion showed that the primary bivariate endpoint of change in serum creatinine and body weight was worse at 96 hours in the ultrafiltration group (Bart et al, 2012). This was driven by a deterioration in renal function, as weight loss was similar. However, the creatinine level was below baseline in both groups at 30 and 60 days, and mortality and re-hospitalization rates were also similar. A higher percentage of patients in the ultrafiltration group had a serious adverse event (72 *vs* 57%, *P*=0.03) over 60 days follow up, mainly as a result of higher incidence of renal impairment, bleeding and intravenous catheter-related complications.

As a result the CARRESS-HF trial has tempered enthusiasm for ultrafiltration in patients with significant renal impairment, although it is important to understand the limitations of the study and need for further research. The patient population included were not diuretic resistant, with average urine output >2.8 litre/day on medical therapy. In addition, the rise in serum creatinine (20.3 ± 61.9 µmol/litre) is not necessarily clinically relevant in this group of patients (Wen et al, 2013). The pharmacotherapy arm were treated in an aggressive and dynamic manner, with furosemide doses of up to 30 mg/hr in addition to metolazone 5 mg twice a day, and intravenous positive inotropes and vasodilators where needed. In comparison, ultrafiltration was performed without inotropes at a fixed fluid removal rate of 200 ml/hr which may be excessive (Kazory, 2013) and in clinical practice should be titrated to clinical response (Bart et al, 2005). Lastly, rates of intravascular volume refill were not monitored. Another single centre experience in patients using ultrafiltration as a rescue therapy in patients with cardio-renal syndrome refractory to medical therapy showed relief of congestion and significant haemodynamic improvement without a significant deterioration in renal function (Patarroyo et al, 2012).

It is clear that in both studies adverse clinical event rates are high, emphasizing the need for a better understanding and treatment of the cardio-renal syndrome and careful patient selection. CARRESS-HF would suggest that significant pre-existing renal impairment is a relative contraindication to ultrafiltration. A current randomized trial (AVOID-HF), due for completion in 2014, is comparing rates of hospitalization between patients with acute heart failure without significant renal impairment treated with either intravenous diuretics or ultrafiltration.

The future of ultrafiltration

A circuit used for ultrafiltration typically lasts for up to 3 days at a cost of approximately £600, and therefore is more efficiently used in patients with significant fluid overload. However, there is the potential that future circuits may become available for shorter duration of use, increasing applicability to a wider heart failure population.

As with all new medical technology, it would also be expected that costs would reduce in the longer term as sales and use increases, while production costs and tenders improve. In addition, changing to peripheral rather than central venous access, moving patients from high dependency units to general wards or even an outpatient setting would all help to further reduce the cost and increase the availability of ultrafiltration.

Conclusions

Heart failure is extremely common, and is associated with significant morbidity and mortality. Fluid overload is a frequent complication of advanced heart failure, which is sub-optimally treated in a significant subset of patients as a result of diuretic resistance, often resulting in prolonged and repeated hospitalization. There is therefore a need for an alternative therapy. Ultrafiltration is a safe, useful adjunct in the management of advanced heart failure, offering improved weight loss and haemodynamics compared to standard medical therapy. Contemporary equipment and treatment regimens are cost effective, reducing length of hospital stay and readmission rates. **BJHM**

Figures 1–3 *are reproduced courtesy of Gambro.*
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KEY POINTS

- Fluid overload is a frequent complication of advanced heart failure which impacts on disease progression and is associated with increased morbidity and mortality.
- Treatment options are limited, and drug therapy is sub-optimal in a significant subset of patients as a result of diuretic resistance.
- Ultrafiltration works by using hydrostatic pressure to force blood against a semi-permeable membrane, and has a key advantage of maintaining complete control over the rate and total volume of fluid removed.
- Ultrafiltration is recommended by international cardiology guidelines to reduce fluid overload in selected heart failure patients.
- Contemporary equipment and algorithms are cost effective, and superior to diuretic therapy at reducing length of hospital stay and re-admission rates.

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