

Acute Dialysis Quality Initiative

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Workgroup 4

Hemofiltration in Cardiac Surgery and Heart Failure

Robert Bartlett

*William R. Clark**

Emil Paganini

Geoffrey Sheinfeld

Introduction

One of the most common “non-renal” applications for extracorporeal blood purification is in the management of heart failure (HF). In this workgroup report we will summarize the existing literature concerning HF, with special attention paid to the importance of concomitant renal failure. The bulk of our consensus work focuses on the use of extracorporeal ultrafiltration for the treatment of HF. In addition to providing a critique of existing work in this area, specific recommendations for future research into this relatively new, and potentially important, therapeutic option for HF patients are proposed.

How is heart failure defined and classified?

A broad definition of HF is cardiac dysfunction related either to impaired ventricular filling or reduced ventricular pumping of blood (1). Specifically, guidelines published by a joint American College of Cardiology/American Heart Association task force define heart failure as a “complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.” Furthermore, the guidelines state that “because not all patients have volume overload at the time of initial or subsequent evaluation, the term ‘heart failure’ is preferred over the older term “congestive heart failure”.

Clinical Classification of heart failure

Although chronic HF is the most common form of this disorder, it is important to recognize that other forms exist. In Table 1, a classification scheme proposed by the ADQI Work Group appears. In this scheme, HF has three distinct classes. The first class stems largely from the clinical observation that mortality in the intensive care unit is directly related to the degree of volume overload. Specifically, several studies have demonstrated that weight gain of greater than 10% of baseline weight is associated with

increased mortality, relative to weight gain of smaller magnitude. Weight gain >10% occurs most commonly after aggressive volume resuscitation for a variety of disorders frequently associated with severe hypotension, including sepsis, pancreatitis, burns, and trauma. Many of these disorders are associated with a generalized vascular permeability disturbance (“capillary leak”) resulting in an inability to maintain intravascular volume despite seemingly adequate volume repletion. In addition, intraoperative hemodynamic instability with prolonged hypotension may necessitate large volume resuscitation both in the operating room and in the immediate post-operative period. In this setting, volume management becomes particularly problematic if the intraoperative hypotension leads to acute tubular necrosis.

Table 1: Proposed classification for Heart Failure

Class I: Critically ill patients with volume overload
Ia: 5-10% (volume expansion relative to baseline body weight)
Ib: 10-20%
Ic: > 20%
Id: organ dysfunction (e.g. pulmonary, liver, gut, brain, renal) on basis of volume overload
Class II: Acute heart failure (with or without renal failure)
IIa: Post-cardiac surgery
IIb: Other causes (e.g. acute coronary syndrome, myocarditis, thoracic trauma)
Class III: Chronic heart failure
IIIa: Stable
IIIb: Acute decompensation

De novo heart failure represents the second class defined by the work group. Specific clinical scenarios falling in this category include acute myocardial infarction, acute mitral regurgitation due to a ruptured chorda tendina and acute aortic insufficiency due to a “flail valve” or endocarditis. In these situations, the underlying pathophysiology of the heart failure syndrome is significantly different from that which occurs in chronic heart failure (see below). Specifically, in acute HF, the adaptive mechanisms that can sustain cardiac output for long periods of time in chronic HF do not have time to develop. Consequently, patients in this category typically develop cardiogenic shock requiring urgent therapy, including vasopressors and, most importantly, surgical intervention.

The third category in the ADQI classification scheme is chronic HF. The rest of this report addresses this category, including the pathophysiology of chronic HF and the potential therapeutic benefit of extracorporeal ultrafiltration (UF) for acute exacerbations.

Consensus statement: There is consensus that the guidelines for defining HF published by the joint American College of Cardiology/American Heart Association task force be adopted. We further propose a 3-category classification scheme for HF shown in Table 1.

What is current practice for management of chronic heart failure?

Approximately five million people in the United States (US) currently have the diagnosis of chronic HF, which has a prevalence of ten per 1000 in the elderly population (age > 65 yrs). This disorder is responsible for nearly 1,000,000 hospitalizations and 300,000 deaths per year (2). As opposed to many other cardiovascular disorders, the incidence of HF is increasing and it is estimated that more than 500,000 new cases of HF are now diagnosed annually (2, 3). The total annual cost of caring for patients with chronic HF in the US may be as high as 40 billion dollars, most of which is incurred in the hospital setting. These figures are staggering, especially in light of the recent advances that have been made in the understanding of HF pathophysiology.

Pathophysiology and clinical manifestations of chronic heart failure

The clinical manifestations of HF may be related either to fluid retention/congestion (edema and dyspnea) or reduced cardiac output (fatigue and renal insufficiency). Most cases of HF in the US are primarily due to coronary artery disease (3). However, irrespective of the underlying etiology, mechanisms that initially provide adaptive benefit to the structurally changing heart in HF eventually form the basis for the pathophysiology that characterizes advanced HF. This pathophysiology includes neurohormonal stimulation (4), cardiac remodeling (5), and possibly inflammatory mechanisms (6). Specific neurohormonal elements that are activated include the adrenergic system, the renin-angiotensin-aldosterone-system (RAAS), and the hypothalamic-neurohypophyseal system (7). The specific pathophysiologic by-product of the latter system is arginine vasopressin, which results in both vasoconstriction and free water retention (8). A counter-regulatory response to these effects of vasopressin is release of a family of natriuretic peptides both by the heart and by the brain, including brain natriuretic peptide (BNP) (9-12). This compound has both diagnostic and therapeutic potential in HF patients.

Non-pharmacologic therapy of CHF includes salt and water restriction for all patients, electrical therapy for patients with concomitant arrhythmias, and surgical therapy for patients with specific indications, such as coronary artery or valvular disease (13). However, the mainstay of HF therapy is pharmacologic management, which has been modified in recent years based on the results of large interventional trials. Standard-of-care is now considered the combination of an ACE inhibitor (and diuretic, or combination of diuretics) as first-line therapy for all symptomatic HF patients with reduced systolic function and for asymptomatic HF patients with documented left ventricular dysfunction (1, 13). Addition of a beta-blocker, except in patients with contraindications, is also recommended (1, 13). Two other agents with documented utility are digoxin and spironolactone (1, 13). On the other hand, therapies that do not appear to provide clinical benefit are calcium blockers, oral inotropes, systemic vasodilators, and anti-cytokine

agents (13). A possible exception to this is nesiritide, a recombinant brain natriuretic peptide shown to have clinical utility in recent trials (11, 12).

Despite the benefits of the above agents, HF therapy is not without adverse effects, especially in patients falling in New York Heart Association (NYHA) classes III and IV (14). In many of these patients, hypotension often precludes use of fully therapeutic doses of ACE inhibitors and beta blockers. Moreover, for a patient with advanced HF, blood pressure is quite variable since it is influenced directly by cardiac output, which in turn is modulated by filling pressures in accordance with Starling's law (15). Another problem that commonly develops is diuretic resistance (16). Many patients with advanced HF have "functional" renal insufficiency in which reduced cardiac output leads to decreased glomerular filtration but intact renal tubular function. Since the efficacy of most diuretics is dependent upon entry into the renal tubular lumen via glomerular filtration, their function is impaired in advanced HF. Although larger diuretic doses may achieve the desired effect, the well-described adverse effects of diuretics, especially those related to electrolyte and acid-base disturbances, are much more likely to occur at such doses (17). These disturbances, especially hypokalemia, hypomagnesemia, and metabolic alkalosis, are particularly worrisome in this patient population characterized by a high incidence of cardiac arrhythmias. In addition, diuretics may induce effective intravascular volume depletion, potentially exacerbating both hypotension and hyponatremia and resulting in worsened renal function.

Consensus Statement: There is consensus that chronic HF is a major public health problem and while there have been significant advances in the management of chronic HF, primarily drug-therapy, significant morbidity and mortality exists with this condition. The evidence base for the pharmacologic management of chronic heart failure has been reviewed elsewhere (13). By contrast the use of ultrafiltration has undergone only limited scrutiny and little is known about the role of this modality in concert with drug therapy.

What are the unique aspects of renal function in the setting of heart failure?

A number of issues complicate the assessment of renal function in patients with HF. Some of these issues relate specifically to the use of the serum creatinine as an estimate of renal function (18,19). Because HF is primarily a disease of the elderly, reliance upon the serum creatinine as an estimate of renal function can be very misleading in this patient population. Therefore, even before considering the direct HF-related effects on renal function itself, the relationship between age and GFR must be considered. Moreover, as is the case for many chronic illnesses, malnutrition with loss of lean body mass, possibly as a result of "cardiac cachexia", may be significant in HF patients. Because creatinine generation and, therefore, the serum creatinine is a function of lean body mass at any GFR (20), renal function may be overestimated by assessing an isolated serum creatinine. Finally, at any GFR, the volume overload that is nearly always present in an acute HF exacerbation also has a depressive effect on the serum creatinine through hemodilution.

Although use of the serum creatinine is obviously problematic, attempts to assess renal function by estimating GFR rather than simply using the serum creatinine are also fraught with difficulty in the HF patient population. The anthropometric equations used typically to estimate GFR, such as the Cockcroft-Gault (18) and MDRD (19) equations, were validated in relatively stable patients with chronic renal insufficiency. Both equations require body weight as an input, which is assumed to be “dry weight”. Obviously, the vast majority of patients with an acute HF exacerbation do not fulfill this criterion and use of both of these equations leads to an overestimation of actual GFR. Moreover, a fundamental assumption underlying the use of these equations is that a steady state situation with respect to renal function exists. However, renal function in the setting of HF is a dynamic situation because, as indicated above, “functional” renal insufficiency occurs due to impaired renal perfusion. Therefore, renal function in HF is highly dependent on the severity of the HF in a given patient and improvement in cardiac function leads to a concomitant increase in GFR. However, numerous possible “non-functional” causes of acute renal failure are also relevant in the typical HF patient. These include pre-renal impairment from overly aggressive diuresis, hemodynamically-mediated compromise from HF medications (e.g., ACE inhibitors), and acute tubular necrosis from prolonged effective volume depletion.

Recent data suggest strongly that the degree of renal function impairment influences the outcome of HF patients (21-25). Weinfeld and colleagues (21) followed renal function in 48 patients admitted for exacerbation of advanced HF. All patients received diuretic therapy and sustained a minimum weight loss of 2 kg during the hospitalization. Acute renal dysfunction (ARD) was defined as an increase in the serum creatinine of greater than 25% over baseline to a value of greater than 2.0 mg/dL. Relative to patients with relatively preserved renal function, patients fulfilling these ARD criteria were found to have a significantly longer hospital length of stay (17 vs. 9 days, $p = 0.02$) and higher risk of death (relative mortality risk=5.5, $p = 0.002$). Although patients at risk could not be identified easily from baseline characteristics, two clear risk factors were advancing age and lower baseline GFR. These investigators concluded that declining renal function frequently precludes optimal HF management and therapeutic options are limited for patients who develop this complication.

Hillege et al. (22) have also provided recent evidence that impaired renal function in HF patients has a negative prognostic effect on survival. Using the Cockcroft-Gault equation to estimate GFR, these investigators attempted to isolate the effect of renal function, relative to other established risk factors, on survival in 1906 HF patients participating in the PRIME-II Study (26). As opposed to the situation during a HF exacerbation, renal function in this study was assumed to be at a relatively steady state level because it was estimated at the time of enrollment into the study. Consequently, the Cockcroft-Gault equation was a reasonable approach in this study. In a multivariate analysis, the risk factors most strongly predictive of mortality were high NYHA class, use of an ACE inhibitor, β -blocker, or digitalis, low systolic blood pressure, low serum sodium, history of myocardial infarction, and low baseline GFR. Use of an ACE inhibitor, NYHA class, and baseline GFR were found to be the strongest predictors, with patients having an estimated GFR less than 59 mL/min at a significantly higher risk of death than those with better kidney

function. Moreover, NYHA Class IV patients with an estimated GFR in the lowest quartile (less than 44 mL/min) had the highest risk of death.

Consensus statement: There is clear evidence that HF affects not only renal function but also the standard measurements of renal function. Caution is advised on the use of serum creatinine, especially as a single measurement, in the setting of HF. Nonetheless, renal dysfunction is common in the setting of HF and portends a poor prognosis.

What are the clinical and technical considerations for the use of extracorporeal blood purification in patients with heart failure?

Both isolated ultrafiltration and hemofiltration with or without dialysis have been used in patients with acute decompensation of HF, with and without overt renal failure.

Ultrafiltration vs. hemofiltration

Although useful for volume removal in the management of “isolated” fluid overload (27), isolated ultrafiltration (UF) is not effective as a blood purification modality for the following reasons. First, the concentrations of small solutes are effectively the same in the ultrafiltrate and the plasma water. Although net mass removal from the body is achieved in the ultrafiltrate, the fraction of the total body solute mass removed is the same as the fractional removal of plasma water. Since fractional mass removal of solute and plasma volume reduction occur proportionately, small solute concentrations in the plasma do not change significantly in isolated UF. On the other hand, the ultrafiltrate concentrations of larger solutes having restricted transmembrane passage are less than their simultaneous plasma water concentrations due to partial or complete exclusion by the membrane. Thus, fractional mass removal in the ultrafiltrate is proportionately less than plasma volume reduction, resulting in a net increase in the blood concentrations of larger sized molecules.

On the other hand, hemofiltration involves the simultaneous removal of plasma water by UF and replacement with a buffered electrolyte solution (replacement or substitution fluid) (30). Since the ultrafiltration rate used in hemofiltration may be as high as 400 mL/min, one obvious function of the replacement fluid in hemofiltration is volume preservation in the patient. The difference between this (absolute) ultrafiltration rate and the replacement fluid rate is the net ultrafiltration (weight loss) rate. However, the use of replacement fluid differentiates hemofiltration from isolated UF and accounts for the fact the former is a blood purification modality while the latter is not. In hemofiltration, replacement fluid administration results in the dilution of non-filtered toxins remaining in bloodstream and an associated reduction in blood concentrations. This dilution phenomenon accounts for hemofiltration’s effectiveness as a renal replacement therapy.

Overview of the use of isolated ultrafiltration for acute exacerbations of chronic heart failure

Due to the underlying pathophysiology of HF, the therapeutic range in which the pharmacologic agents considered standard of care can work is small and titration in this narrow range is difficult. Indeed, it is not uncommon for this titration process to take several days in the hospital. Moreover, a significant proportion of this process may occur in an intensive care setting. Clearly, conventional medical therapy has limitations, and an additional therapeutic alternative that addresses these limitations is desirable. A potential alternative to this is UF.

Isolated UF as a therapy for volume overload was first described formally by Silverstein and colleagues in 1974 (27). Employing a blood flow rate of 200 mL/min and a 1.0 m² filter, these investigators reported ultrafiltration rates of up to 800 mL/hr could be tolerated, as determined by the degree of volume overload and hemodynamic status of an individual patient. Subsequent studies (29-43) have characterized UF's specific clinical benefits, which include decreases in cardiac filling pressures and improvements in diuretic responsiveness, hyponatremia, edema, renal function, and dyspnea. A common element of many of these studies has been the ability of UF to "reset" the neurohormonal axis, as evidenced by decreases in plasma norepinephrine, aldosterone, and renin activity. A relatively common prescription in these studies has been an ultrafiltration rate of 300-600 mL/hr, administered over a several hour treatment period for consecutive days.

Physiologic and clinical considerations in the use of ultrafiltration for heart failure

In UF, removal of plasma water is achieved by application of a pressure gradient across an extracorporeal membrane. This pressure gradient can be generated by creation of a positive pressure in the blood compartment or a negative pressure in the ultrafiltrate compartment the filter. Modern devices control transmembrane pressure automatically to achieve the desired rate and volume of ultrafiltrate production. Extracorporeal UF is a dynamic process in which the rate of volume removal by the extracorporeal filter has to be viewed in the context of the manner in which it modifies Starling's forces governing fluid flow across the capillary wall. First, removal of plasma ultrafiltrate from the intravascular space decreases hydrostatic pressure in that compartment. This results in a hydrostatic pressure gradient across the capillary wall that favors entry of fluid from the extravascular (interstitial) space, which has a relatively high hydrostatic pressure due to tissue edema. Because the ultrafiltrate generated is relatively protein-free, another UF-induced Starling's force change promoting capillary refill is an increase in oncotic pressure in the intravascular compartment.

A fundamental question relating to the use of UF is the rate at which volume can be removed while maintaining hemodynamic stability, an important determinant of which is blood volume. Provided the rate of removal from the intravascular compartment does not exceed the capillary refill rate, maintenance of blood volume is possible. Marenzi and colleagues (42) estimated capillary refill to be at least 800 mL/hr at the initiation of an UF treatment, falling to 400 mL/hr at the conclusion of a treatment achieving

approximately 4 L of volume removal. This figure is consistent with ultrafiltration rates reported in other published studies demonstrating clinical benefits of UF therapy.

One of the above cited studies provides insight into the potential mechanisms explaining the benefits of UF in patients with HF. Agostoni et al measured neurohormonal and clinical parameters in NYHA class II and III patients treated either with high-dose intravenous furosemide or a single extracorporeal UF treatment (36). Ultrafiltration was performed at a rate of 500 mL/hr and achieved a cumulative volume removal of 1.7 L, which was similar to the urine volume in the diuretic-treated group during the study time period. In the UF group, a significant decrease in plasma aldosterone, norepinephrine, and renin activity was observed within 48 hrs, along with an improvement in hyponatremia. Moreover, a significant improvement in functional capacity that persisted for three months occurred. On the other hand, these changes did not occur in the diuretic group, as elevated filling pressures and pulmonary congestion instead recurred within days. The clinical benefits reported in this study may relate to the difference in the composition of the volume removed by UF vs. diuretics. In UF, the fluid removed is an ultrafiltrate of plasma and, as such, has electrolyte concentrations that are isotonic with respect to plasma water. On the other hand, urine inherently is hypotonic with respect to plasma water. Therefore, sodium removal is significantly greater in ultrafiltrate relative to the same volume of urine. Moreover, due to the isotonicity of the ultrafiltrate, UF induces no acute changes in electrolyte concentrations.

Although several investigations suggest UF provides therapeutic benefit in severe HF, these studies have been small and largely uncontrolled. Moreover, a recent preliminary study suggested no benefit in a group of diuretic-resistant patients with relatively advanced renal insufficiency at the time of UF initiation while more favorable clinical results were seen with same device in a group of patients having less advanced renal insufficiency (personal communication: Dr Margaret Redfield). In this study, extracorporeal UF using the CHF Solutions System 100 was applied in 11 elderly patients (mean age, 70 yrs) with a mean serum creatinine of 2.2 mg/dL (estimated mean GFR of 40 mL/min based on “dry” body weight). The goal of therapy was to achieve a net volume removal of 4 L over an eight hour time period. A total of 31 UF treatments (mean of 2.8 treatments per patient) were delivered to this patient group over an average period of five days. In the majority of patients, renal function deteriorated to the point that, in the judgment of the investigators, seven of the patients required some form of dialysis therapy to control uremia. .

Consensus statement: While useful in the removal of excess fluid, isolated UF is not a blood purification technique, having no net effect of small molecule concentrations in the plasma and actually concentrating larger molecules. Although numerous benefits have been proposed for UF, clinical evidence of benefit has been limited to small, uncontrolled (Level IV and V) studies.

What questions should be addressed by future studies of ultrafiltration and hemofiltration in the management of heart failure?

Although the available clinical data suggest a role for UF in the management of patients with HF, a number of issues need to be addressed before UF becomes a “mainstream” therapy in this population (Table 2). One critical issue relates to the technical requirements for an extracorporeal system used specifically in HF. Although the basic mechanism by which volume removal occurs (i.e. creation of a pressure gradient across a membrane) is similar to that in other extracorporeal therapies, devices used for HF patients may require additional features. Device size and portability represent two such features. Standard machines used for conventional hemodialysis and, in most cases, continuous renal replacement therapy (CRRT) were developed largely for applications other than simple volume removal and, as such, are more complex than is necessary for isolated UF in the HF population. Moreover, these traditional devices tend to be relatively large and bulky, making portability difficult. Ease of use by non-dialysis personnel and easy portability between cardiac units, intensive care units, and even outpatient clinics are highly desirable features for a specialized UF device (44-46).

Table 2. Issues to be addressed by future studies of ultrafiltration/hemofiltration in patients with heart failure

- Device portability and ease of use
- Venous access: central or modified PICC line
- Modality: continuous vs. intermittent daily UF
- Cost-effectiveness (effects of hospital length of stay, readmission rate)
- Close collaboration between nephrologist & cardiologist
- Clinical data requirements for therapy adoption

Another important consideration is the type of vascular access required by the system. When conventional hemodialysis and venovenous CRRT systems are used in the acute dialysis setting, a central venous catheter is nearly always chosen as the vascular access. An important consideration in the use of such an access is the achievable blood flow rate because of this parameter’s significant effect on solute clearances in the therapies delivered by these systems. In general, the desired solute clearances for these therapies can only be achieved with relatively high blood flow rates (≥ 150 mL/min), the attainment of which requires a large-bore catheter in a central vein. However, isolated UF is not a blood cleansing modality and solute clearance is not a relevant consideration (47). This suggests the possibility of using a smaller bore catheter in a peripheral vein for vascular access. From one perspective, the minimum blood flow rate is that required to avoid excessive hemoconcentration. To quantify this phenomenon, the filtration fraction (ratio of the

ultrafiltration rate to the plasma flow rate delivered to the filter) has been employed traditionally. In general, a maximal filtration fraction of 35-40% usually guides prescription in acute post-dilution hemofiltration, which is the relevant comparison in this instance. At filtration fractions beyond this range, hemoconcentration is associated with an environment which promotes interactions between both formed elements and proteins in the blood and the filter membrane, leading to a high risk of filter clotting. However, the UF rates typically employed in isolated UF (less than 10 mL/min) are significantly less than those in hemofiltration, which may be 40 mL/min or higher. Therefore, while the minimum blood flow rate may be 200 mL/min or higher in the setting of post-dilution hemofiltration, a blood flow rate of 50 mL/min may be adequate to maintain the filtration fraction less than 30-40% in isolated UF. For example, based on a blood flow rate of 50 mL/min prescribed to a patient with a hematocrit of 35%, isolated UF at a rate of 10 mL/min (600 mL/hr) results in a filtration fraction of 28% at the onset of therapy.

Although the above analysis suggests a blood flow rate as low as 50 mL/min may be used in isolated UF, two caveats must be discussed. First, the filtration fraction calculation above is based on a hematocrit of 35% *at the start of therapy*. However, as UF proceeds and net volume removal occurs, hematocrit increases. Therefore, for a given volume of blood flowing through the filter, an increasing percentage of that volume is comprised of red blood cells and a decreasing percentage is comprised of plasma water during ongoing UF therapy. At a fixed blood flow rate and UF rate, this implies an increasing filtration fraction, since plasma water flow rate is the denominator in the filtration fraction equation. Thus, from the relatively narrow perspective of filtration fraction, a seemingly adequate blood flow rate at the onset of UF may be inadequate after several hours of therapy. A second important consideration related to blood flow rate involves another effect that it has on filter membrane performance. The velocity that blood achieves while passing through an individual hollow fiber membrane is directly proportional to its blood flow rate (48). In turn, the velocity (or more rigorously, the velocity gradient) of blood at the membrane surface is directly proportional to its “shear” rate at that interface. This parameter is effectively a measure of blood’s ability to “sweep” the membrane surface, thus preserving the filtration capabilities of the membrane. When continuous arteriovenous therapies were popular in the early years of CRRT, filters were designed specifically to overcome some of the drawbacks of the characteristically low blood flow rates achieved with these therapies. However, the design characteristics of contemporary filters are based on the higher blood flow rates achieved with continuous venovenous therapies. Thus, whether or not contemporary filters can achieve adequate ultrafiltration rates at blood flow rates delivered from a peripheral venous access (i.e., approximately 50 mL/min) will need to be assessed carefully.

Finally, a critical factor defining the future role of UF therapy for HF is the design and implementation of clinical trials. In the field of cardiology, the bar has been set very high with respect to clinical data necessary for the adoption of a new pharmaceutical or device. Nevertheless, for several reasons, extracorporeal UF has the opportunity to be incorporated into the therapeutic regimen for many HF patients. First, because the therapy involves a medical device, the clinical trial data requirements are inherently less than those for a pharmaceutical. Second, isolated UF is but one component of a broad

spectrum of therapies falling in the dialysis category and, as such, is not a new therapy. Moreover, with respect to the devices used for isolated UF, either the same or very similar “predicate” devices have been used extensively in the past and most dialysis practitioners have significant experience with isolated UF in both the acute and chronic renal failure settings.

One of the most important aspects of future clinical investigations of isolated UF for HF is defining clinical and resource utilization endpoints. Potential clinical endpoints include those based on pre-determined hemodynamic targets (49-52), such as pulmonary capillary wedge pressure or cardiac index, volume removal, such as the time required to meet a defined volume target, and changes in neurohormonal parameters. Other clinical endpoint considerations include the effect of UF on diuretic and vasoactive medication usage and treatment-related adverse effects, such as arrhythmias, electrolyte disturbances, renal dysfunction, and myocardial ischemia. Importantly, cost-effectiveness parameters, including intensive care unit and hospital length of stay and re-admission rates, need to be evaluated, along with the effect of UF therapy on quality of life. Finally, it is anticipated that these studies will involve a spectrum of UF prescriptions with respect to flow rates and both treatment frequency and treatment duration.

Consensus statement: Finding a practical, economical alternative for the management of patients with HF is essential based on the economic implications of treating the rapidly growing HF population in the hospital. Published literature suggests isolated UF has the potential to significantly impact morbidity, quality of life, hospital length of stay, and hospital re-admissions for HF patients (Grade D). However, broader adoption of this therapy requires larger, randomized clinical studies to characterize the extent of benefit obtained from UF.

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Authors:

In alphabetic order.

Robert Bartlett, MD. Department of Surgery, University of Michigan, Ann Arbor, MI.
Email: robbar@med.umich.edu

William R. Clark, MD. Nephrology Division, Indiana University School of Medicine, Indianapolis, IN.
Gambro Renal Products, Intensive Care Lakewood, CO. Email: William.Clark@us.gambro.com

Emil Paganini, MD. Extracorporeal Dialysis Section, Cleveland Clinic Foundation, Cleveland, OH. Email: paganie@cesmtp.ccf.org

Geoffrey Sheinfeld, MD. McKay-Dee Hospital Center, Ogden, UT. Email: mkgshain@ihc.com

Consultants:

David Weinstein, MD. Extracorporeal Dialysis Section, Cleveland Clinic Foundation, Cleveland, OH.
Email: weinstd@cesmtp.ccf.org