Abstract—Heart failure and chronic kidney disease share a number of risk factors and pathophysiological pathways. These 2 pathological processes coexist in large numbers of patients. Whereas the presence of chronic kidney disease in patients with heart failure adversely influences their survival, cardiovascular disease is the major cause of mortality in individuals with chronic kidney disease. The management of heart failure by cardiologists has recently expanded from pharmacological treatment to extracorporeal strategies; the interaction between (and concurrent use of) these approaches traditionally has been part of nephrology care and training. The purpose of this review is to explore these management strategies from a nephrologic standpoint and cover the pathophysiology of diuretic resistance, new pharmaceutical strategies to induce natriuresis or aquaresis, and the physiological basis and theoretical advantages of fluid removal by nontraditional peritoneal or hemofiltration approaches. This review also focuses on the technical features, safety, and potential risks of dedicated ultrafiltration devices that do not require dialysis staff or facilities and that are now readily available to nonnephrologists. (Circulation. 2008;117:975-983.)

Key Words: diuretics ■ extracorporeal circulation ■ heart failure ■ natriuretic peptides ■ pharmacology

Our understanding of the pathophysiology of heart failure (HF) and the development of new therapeutic strategies are rapidly evolving. It is now appreciated that HF and chronic kidney disease (CKD) share a number of risk factors and pathophysiological pathways (eg, activation of the renin-angiotensin-aldosterone system [RAAS]) and have a causal relationship (ie, the role of CKD as an independent cardiovascular risk factor). Indeed, by necessity, cardiologists have become adept at the management of refractory volume overload, complex diuretic regimens, dysnatremias, and hemodynamic causes of acute renal failure. In addition to pharmacology advances, technology for extracorporeal ultrafiltration has been newly introduced and is advocated for use by nonnephrologists. This represents a major paradigm shift away from the traditional hemodialysis or peritoneal dialysis (PD) modalities for fluid removal.

Despite practical and theoretical advantages of some of these newer treatment strategies, some can potentially be harmful to the patient. This is especially true in the case of the mechanical pumped blood ultrafiltration devices that can worsen renal function or be subject to potentially serious or lethal complications. It is the purpose of this article to address these concerns from a nephrologic perspective, highlighting the pathophysiology and benefits of recent pharmacological approaches, as well as detailing practical aspects and pitfalls related to use of these extracorporeal ultrafiltration devices.

The different therapeutic tools (eg, aquaretics, diuretics, isolated ultrafiltration, and PD) are to be considered different steps of a strategy in which they have complementary or sequential, rather than competitive, roles in the care of this large patient population. The principal sites of action of these therapeutic options are summarized in Table 1.

HF remains the single most common reason for admission among patients aged >65 years, and its direct and indirect costs were estimated at $30 billion in 2006.1,2 Most patients are admitted with fluid overload, often diuretic resistant and typically in the setting of cardiomyopathy. CKD and ischemic cardiomyopathy share a number of major risk factors, including hypertension and diabetes mellitus.3 Moreover, it has been shown that kidney dysfunction per se is a risk factor for developing HF both in middle-aged adults and in the elderly,4,5 and thus they are comorbidities present in a large portion of patients. The term cardiorenal syndrome has been applied to the presence or development of renal dysfunction in patients with HF.6 In a study by de Silva et al7 of 1216 patients with chronic stable HF, only 7% of the patients had an estimated glomerular filtration rate of 90 mL/min, with 83% of the patients presenting with stage 2 or 3 CKD (glomerular filtration rate of 60 to 89 or 30 to 59 mL/min per 1.73 m², respectively). CKD carries a poor prognosis in these patients. It has been shown that the glomerular filtration rate in patients with HF is the most powerful predictor of mortality, exceeding functional status and ejection fraction.8 Finally, as described below, many patients admitted to the hospital for decompensated HF develop either de

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Release of antidiuretic hormone (ADH) increases in patients with HF because of reduced activation of mechanoreceptors located on the high-pressure side of the circulation. Two types of ADH (or vasopressin) receptors have been identified: V1 (V1a, V1b) and V2. ADH increases blood volume by promoting free water retention through the V2 receptors in renal cortical collecting ducts. It can also lead to vasoconstriction and possibly cardiac hypertrophy via V1a receptors.

Antidiuretic hormone receptor antagonists are considered maladaptive responses that are central to the pathophysiology of HF. ADH receptor antagonists (“aquaretics”) were originally used for the correction of hyponatremia in the context of syndromes of inappropriate ADH secretion or cirrhosis and are potentially capable of ameliorating fluid overload in HF patients through excretion of electrolyte-free water. Compared with diuretics, ADH antagonists have the theoretical advantage of correcting hyponatremia, an independent predictor of mortality in patients with HF.

The 2 most extensively investigated ADH antagonists are conivaptan (a dual V1a/V2 receptor antagonist) and tolvaptan (an oral, selective antagonist of the V2 receptor). Recently, the results of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trials in acute decompensated HF were published. These large, randomized, double-blind, placebo-controlled studies tested the benefit of tolvaptan in 3 clinical trials: 2 identical short-term and 1 longer-term safety and outcome protocols. The aggregate findings demonstrated that tolvaptan, used in addition to standard therapy (including diuretics), relieved certain symptoms without adverse effect on renal function; however, it did not decrease mortality or HF-related morbidity at 1 year. Hypotension, when present, was also improved. Although these studies showed modest symptomatic relief with no major adverse effect, lack of a beneficial long-term impact on mortality and morbidity makes it unlikely that ADH antagonists will become a major or primary part of treatment strategies in patients with decompensated HF in the near future. Currently, only the intravenous formulation is available outside the research setting, and hypotension is potentially problematic because of blockade of the V1 receptor. If the V2-selective oral forms of these medications become available in the United States, it is possible that they will have a role as part of broader treatment strategies.

Diuretics

Even though diuretics are the traditional mainstay of treatment for both chronic and acutely decompensated patients, they are one of the few therapies for HF that have not been subjected to a randomized, placebo-controlled trial. The optimal diuretic dose in either of these clinical situations has been controversial. Although furosemide was reported to be safe at doses as high as 4000 mg/d by some investigators in the past, more recent studies recommend much lower ceiling doses because of potential adverse effects. Practice patterns vary substantially worldwide, and these drugs are being used by clinicians at the upper dose ranges only when their benefits are thought to outweigh the concern for ototoxicity. In general, compared with normal individuals, patients with HF need higher doses of loop diuretics to achieve a similar sodium excretion, and the magnitude of the “maximal” response is attenuated. Resistance to diuretics is a potentially devastating phenomenon and an independent predictor of mortality that can develop as HF progresses. The definition of diuretic resistance has been problematic and hinders interpretation of the older literature: The natriuretic response to a loop diuretic such as furosemide can theoretically be defined by relating the amount of the drug in the urine to the sodium excretion in the same sample. However, most clinical studies have used various diuretic doses (and/or urine volumes) as indices of resistance.

An understanding of the kidney’s normal mechanisms of adaptation to sodium losses has provided a physiological basis for the development of diuretic resistance. The term braking phenomenon applies to the long-term use of diuretics and refers to a decline in the magnitude of natriuresis after administration of sequential doses. The key concept is that the nephron normally autoregulates to maintain sodium homeostasis. “Tubuloglomerular feedback” mechanisms exist that attenuate natriuresis when an increase in tubular sodium load is detected: Sodium clearance is thus reduced back to baseline, and the person is thereby kept in sodium balance. Unfortunately, a therapeutic increase in tubular sodium delivery induced by diuretics elicits these same counterbalancing autoregulatory responses, which are considered maladaptive in the case of HF. Specifically, the primary diuretic response increases sodium delivery to the juxtaglomerular...
apparatus, stimulates renin secretion, enhances the RAAS system, induces hypertrophy and hyperplasia of distal tubular cells, and stimulates the efferent SNS.24 Consistent with a maladaptive neurohumoral response to a pharmacological natriuresis, in Studies of Left Ventricular Dysfunction (SOLVD), Domanski et al27 found that the rates of hospitalization for HF, cardiovascular mortality, and all-cause mortality were higher in patients taking a diuretic than in those who were not. The increased absorption of sodium by the distal tubules attenuates the effectiveness of the medication. This can sometimes be overcome by altering the diuretic regimen by (1) combining thiazide diuretics with loop diuretics (to block increased distal sodium reabsorption), (2) using higher (preferably intravenous) doses of loop diuretics, and (3) using continuous diuretic infusions to avoid the phenomenon of postdiuretic salt retention.28 Importantly, a new class of agents is under development that block the adenosine A1 receptors mainly in the afferent arteriole, in hopes of attenuating the tubuloglomerular feedback mechanism and enhancing diuresis.29,30

The proximal tubules also manifest an autoregulatory increase in sodium reabsorption that can progressively become a major problem over time: With diminishing sodium leaving the proximal nephron, loop diuretics lose their effectiveness. Thus, a benefit sometimes results from simultaneously using agents that act proximally even though in normal situations they are considered weak diuretics. For example, acetazolamide, a proximal tubule diuretic, might partially restore the effectiveness of loop diuretics; however, it should be used cautiously and briefly under close observation because long-term administration can lead to severe bicarbonate losses and worsening metabolic acidosis.

The concept of proximal sodium avidity leading to decreased delivery to the distal (ie, collecting) tubules also provides insight into the role of pharmacological mineralocorticoid blockade in the treatment of HF. In other (noncardiac) sodium-retaining, high-aldosterone disease processes, ultimately a new equilibrium is reached when sodium retention results in an increased filtered load that exceeds the absorptive capacity of the tubule. Importantly, this physiological “escape” from excess aldosterone does not occur in patients with HF.10 Therefore, they continue to retain sodium in response to aldosterone, and, indeed, use of receptor antagonists (ie, spironolactone) is often followed by a substantial natriuresis in these patients.31 During the last decade, there has also been a growing understanding of the adverse effects of aldosterone beyond these tubular phenomena. Through mechanisms different from its effects on epithelial cell transport of sodium and potassium, aldosterone may mediate hypertension and cardiac fibrosis.32,33 In patients with HF, not only is the activity of the RAAS increased, but the action of aldosterone is also more persistent.10 Consistent with this pathophysiological process, evidence for pleiotropic benefits of mineralocorticoid blockade is rapidly emerging. It is now well known, for example, that spironolactone has effects in nonepithelial tissues, including the heart, vasculature, and brain, that are independent of its action on renal tubular cell ion transport.34 The analysis of SOLVD revealed a significantly lower risk for hospitalization and/or death from HF, cardiovascular mortality, and all-cause mortality when a potassium-sparing diuretic was used alone or in combination with a non–potassium-sparing diuretic.27 Spironolactone is now considered a mainstay of treatment in HF patients. In the Randomized Aldactone Evaluation Study (RALES), Pitt et al35 found that adding spironolactone to standard therapy for HF led to a reduction in the risk of death, decrease in the rate of hospitalization, and a significant improvement of symptoms without increasing the risk of hyperkalemia. Eplerone is a novel agent that selectively blocks the mineralocorticoid receptor and not those for glucocorticoids, progesterone, or androgens.36 It has also been shown to reduce morbidity and mortality in patients with acute myocardial infarctions complicated by left ventricular dysfunction and HF.37 However, serious hyperkalemia (serum potassium ≥6.0 mmol/L) was not infrequent. Although the beneficial effects of aldosterone blockade in HF go far beyond the diuretic properties, hyperkalemia due to impaired potassium excretion would be the main concern in these patients. They frequently have concomitant treatment using other medications with the potential side effect of hyperkalemia (eg, angiotensin-converting enzyme inhibitors).

### Natriuretic Peptides

The natriuretic peptide family includes atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), and urodilatin. ANP and BNP are secreted by the heart, CNP is secreted by the endothelium, and urodilatin is synthesized in renal distal tubular cells.38–40 ANP, BNP, and CNP induce vasodilation, increased urinary sodium and chloride excretion, and suppression of the RAAS and SNS.41 After luminal secretion, urodilatin binds downstream to natriuretic peptide type-A receptors in the inner medullary collecting duct, regulating renal sodium and water excretion via intracellular increase in cyclic guanosine monophosphate.42 Because sodium is the major determinant of extracellular fluid volume, it was suggested that these peptides might be useful in the management of acute decompensated HF. Nesiritide, a recombinant form of human BNP, and ularitide, a synthetic form of urodilatin, have been used in this setting.

The preliminary studies on nesiritide suggested its efficacy and safety in the management of decompensated HF,33,44 and it is the only drug specifically approved for this indication.21 Nesiritide has been shown to be associated with improved postoperative renal function in the setting of coronary artery bypass grafting with the use of cardiopulmonary bypass.45 However, other studies, including 2 meta-analyses, did not confirm its safety or efficacy with regard to improvement in renal function or urine output.46,47 Theoretically, nesiritide, in contrast to loop diuretics, should improve renal hemodynamics through suppression of the RAAS and SNS; thus, no adverse impact on kidney function was expected in patients treated with nesiritide. However, worsening renal function was observed more frequently in the nesiritide group.46 and it was also associated with an increased mortality rate within 30 days after its administration.47 Additionally, a double-blind, placebo-controlled, crossover study failed to show any improvement in glomerular filtration rate, effective renal plasma flow, urine output, or sodium excretion with use of nesiritide.48
The Fusion I trial was the first study to evaluate the potential clinical utility of outpatient intermittent nesiritide infusions in patients with HF. It did not show any difference in renal adverse events between 2 different regimens of nesiritide and usual medical therapy alone. Fusion II is a multicenter, randomized, double-blind, placebo-controlled trial designed to further assess the safety, efficacy, and optimal dosing frequency of outpatient nesiritide for patients with advanced HF. Published results are expected in late 2007.

In pilot studies, ultratide demonstrated beneficial effects in decompensated HF with a stimulation of natriuresis and reduction in the pulmonary capillary wedge pressure. A decrease in blood pressure has been reported to be relatively common in studies evaluating the safety and efficacy of short-term infusion of ultratide. Although the preliminary results of studies with ultratide are encouraging, because of its numerous similarities to nesiritide, safety concerns (mainly renal effects) should be evaluated carefully in a randomized, double-blind, placebo-controlled study before its widespread use can be recommended.

## Extracorporeal Ultrafiltration

Isolated ultrafiltration is an area of recent great interest in the nonpharmacological management of HF, especially because of the marketing of small, relatively simple devices that are dedicated to this purpose. Ultrafiltration has been used both in the in-hospital setting of acute decompensated HF and as an outpatient treatment of refractory HF. The main rationale for its use in the acute setting would be rapid correction of fluid overload when standard management (eg, high-dose intravenous diuretics with or without inotrope agents) has been unsuccessful.

Of paramount importance in determining the role of extracorporeal ultrafiltration (with its attendant risks and expense) is whether the claim of its superiority over fluid removal by aggressive diuresis has a physiological basis. Currently, the rationale for use of extracorporeal methodologies in the chronic setting centers on 3 aspects: rapidity, avoidance of maladaptive renal tubular autoregulatory responses, and magnitude of sodium clearance (Table 2). Indeed, part of the logistical difficulty in caring for HF patients is the slow pace of fluid removal during diuretic titrations, which can often greatly prolong hospitalizations. Faster fluid removal might theoretically reduce the risk of further clinical decompensation, cardiac ischemia, arrhythmias, or need for intensive care unit monitoring. In addition, a cost-benefit analysis for hospital resource utilization might in some cases rationalize the use of expensive ultrafiltration devices by virtue of reducing the hospital length of stay. A more cogent approach to justifying ultrafiltration would be based on the underlying physiology: Although not fully investigated, sodium removal by ultrafiltration may be fundamentally different from, and superior to, diuretic therapies by avoiding enhanced sodium delivery to the distal nephron. Hypothetically, this would prevent the tubuloglomerular feedback mechanisms that lead to maladaptive diuretic resistance, stimulation of the RAAS, and activation of the SNS. Furthermore, for similar volumes of fluid removal, ultrafiltration removes more total body sodium (the main determinant of extracellular fluid volume) than do diuretics. Urine produced by diuretics is hypotonic compared with plasma, whereas ultrafiltrate is isonatremic and iso-osmolar. Finally, by choosing a hemofilter with an appropriately high sieving coefficient, the extracorporeal device designed for ultrafiltration can simultaneously clear through convective (ie, by hemofiltration) large molecules that may be biologically active and have an adverse role in the pathophysiology of HF. For example, high-flux membranes can clear moieties in the size range of cytokines, and there could be a theoretical benefit, for example, from removing certain interleukins or tumor necrosis factors.

Although the concept of using ultrafiltration in the management of HF is supported by the aforementioned hypotheses, the long-term outcome of this therapeutic modality has not been explored extensively. It is not yet clear if this therapy can be considered an efficient and safe part of the standard treatment for refractory HF. Although studies tend to show beneficial effects of this therapy, the majority of them have included highly selected small numbers of patients with a relatively short follow-up of 30 to 90 days without a control group. The results of the first large-scale randomized study designed to assess the benefits and safety of ultrafiltration for the management of HF (the Ultrafiltration Versus IV Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure [UNLOAD] trial) was recently published. In this multicenter study, patients hospitalized for decompensated HF were randomized to receive standard care (ie, intravenous diuretics) or ultrafiltration therapy. The ultrafiltration group showed a greater fluid loss at 48 hours compared with the diuretic group, without a change in serum creatinine or blood pressure. During the 90-day follow-up period, the ultrafiltration patients had reduced rates of rehospitalization and unscheduled visits. We have previously discussed potential methodological shortcomings of this study. In brief, the study population seemed to be more stable than typical decompensated HF patients. Because hemodynamic instability is a potential complication of ultrafiltration therapy, selection of a more stable population might have acted in favor of this modality. Furthermore, the 2 groups were not controlled for the total amount of volume loss at the end of treatment. Therefore, the beneficial effects of ultrafiltration in the reduction of rate of rehospitalization might, at least in part, be the reflection of a greater volume loss in this group.

### Table 2. Proposed Advantages of Slow Ultrafiltration Compared With Diuretics

<table>
<thead>
<tr>
<th>Advantage</th>
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<tr>
<td>More rapid removal of fluid and improvement in symptoms</td>
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<tr>
<td>Higher mass clearance of sodium</td>
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<tr>
<td>Decreased risk of electrolyte abnormality (eg, hypokalemia)</td>
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<tr>
<td>Lack of RAAS activation</td>
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<tr>
<td>Lack of neurohormonal (SNS) activation</td>
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<tr>
<td>Removal of proinflammatory cytokines (with potential restoration of responsiveness to diuretics)</td>
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<tr>
<td>Shortened length of stay for HF-related hospitalizations</td>
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<tr>
<td>Decreased rate of readmissions for HF-related hospitalizations</td>
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<tr>
<td>Decreased risk of worsening renal function</td>
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Although the Fusion I trial was the first study to evaluate the potential clinical utility of outpatient intermittent nesiritide infusions in patients with HF, it did not show any difference in renal adverse events between 2 different regimens of nesiritide and usual medical therapy alone. Fusion II is a multicenter, randomized, double-blind, placebo-controlled trial designed to further assess the safety, efficacy, and optimal dosing frequency of outpatient nesiritide for patients with advanced HF. Published results are expected in late 2007.
Overall, because of lack of strong clinical evidence supporting the advantage of costly ultrafiltration techniques, this modality has not yet gained widespread use. We believe, however, that the aforementioned hypothetical advantages of ultrafiltration will prompt more frequent use of this technique and that nonnephrologist clinicians need to be aware of the potential risks inherent to these extracorporeal pumped blood technologies (Table 3). One obvious potential hazard well recognized in the renal literature is overly aggressive fluid removal, which can lead to decreased effective blood volume, hypotension, renal hypoperfusion, prerenal azotemia, and possibly acute renal failure necessitating dialysis. Central to this pathophysiology is whether a mismatch exists between the ultrafiltration rate and the plasma refill rate. Indeed, it has been suggested that the plasma refill rate can be used to guide the rate of volume extraction in patients with HF undergoing ultrafiltration to avoid inadequate decongestion. We have previously described how rapid ultrafiltration can exceed the plasma refill rate, leading to quantifiable hemococoncentration and acute intravascular volume depletion.

Other than excessively high ultrafiltration rates, a number of other safety issues with these machines are in part shared by traditional dialysis and hemofiltration devices, which are discussed below.

### Air Emboli

Of great concern for any pumped blood technology is the risk of air embolus. Air typically enters the extracorporeal circuit on the prepump side of the tubing set because of the negative (vacuum) pressure at that location. Because even small amounts of air embolus can have disastrous or lethal effects, these machines are required to have air detectors and circuitry to immediately stop the pump and clamp the tubing. Nevertheless, despite the sophistication of the sensors, none are foolproof, and this exceedingly rare complication must remain an ongoing concern for the nursing staff and any practitioner offering these treatments.

### Venous Disconnection and Blood Leak

Even with low blood pump rates, an undetected disconnection of the return (venous) blood line can cause severe hemorrhage. This is a well-recognized complication that can occur when the venous needle dislodges or tubing connections loosen. Current technology detects disconnections by a drop in the venous tubing “return” pressure, and this methodology can be unreliable in these slow-flow low-pressure systems. Although an added safety margin is present at low blood pump speeds, undetected hemorrhage remains a real concern with these machines. We are developing alternative electrically based detection technology to overcome these shortcomings, but it is not yet commercially available.

### Hemolysis

Tubing that is defective or mismatched for the rotating pump head assembly can cause hemolysis and potentially severe hyperkalemia. The risk of this occurring with improved technology and low ultrafiltration pump speeds is rare but never totally eliminated.

### Bioincompatibility

Compared with older technologies, ultrafiltration devices that use synthetic polymers have superb biocompatibility and have virtually eliminated the alternative complement activation problem of cytokine release, fever, bronchospasm, and hypotension. However, polyacrylonitrile membranes (which are currently used in hemofilters because of their excellent ultrafiltration characteristics) can cause profound hypotension due to bradykinin activation in patients on angiotensin-converting enzyme inhibitors. These medications must be discontinued before the use of ultrafiltration treatments or alternative membranes (such as polysulfone).

### Allergic Reactions

There can rarely be immunoglobulin E—related reactions (ie, hypotension, bronchospasm) to the ethylene oxide sterilant used in some dialyzers and tubing sets. This problem can be prevented by extensive rinsing of the extracorporeal circuit, or it can be totally eliminated by choosing components that have undergone alternative methods of sterilization (eg, gamma irradiation).

### Blood Leaks Within the Hemofilter

Damage in shipping or handling to the hollow fibers within the hemofilters can lead to blood leaks into the ultrafiltrate. The risk of hemorrhage has been minimized by sensitive blood-leak detectors in the ultrafiltration tubing pathway.

### Ultrafiltration Rate Calibration Problems

Inadvertently high ultrafiltration rates have historically been a major concern in renal replacement and volume-removal technologies, especially with modern high-flux hemofilters that yield large amounts of ultrafiltration from small pressure gradients. Machine errors causing excess fluid removal still rarely occur despite the technological advances of “volumetrically” controlled ultrafiltration (ie, sealed fluid-filled balancing chambers), redundant scales weighing the ultrafiltrated fluid, and protocols necessitating manual machine calibration.

### Vascular Access–Related Problems

Newer ultrafiltration-dedicated machines are appealing in that some have blood flow rates low enough (<50 mL/min) to use small-caliber needles in peripheral veins. However, a substantial portion of these HF patients will not have veins appropriate or durable for these therapies and will need...
peritoneal ultrafiltration cannot be recommended as first-line therapy for management of acute volume overload and decompensated HF.

A similar paucity of evidence exists supporting the use of PD in the setting of chronic stable HF in patients without end-stage renal disease, limited to case reports and small studies. Overall, most of these investigations point to a reduction in rehospitalization rate and improvement in functional capacity. For example, Gotloib et al reported 20 patients with severe HF refractory to optimal pharmacological therapy. They were initially treated by 2 to 5 sessions of venovenous hemofiltration, followed by the initiation of automated PD (3 sessions per week). After 1 year, all patients showed improvement in cardiac index, thoracic fluid content, New York Heart Association functional class, and rehospitalization rate.

Although the use of PD to treat HF in patients with end-stage renal disease is conceptually appealing, the data are insufficient and contradictory. A study by Takane et al of 16 patients with HF newly started on PD showed benefits in terms of lowering systolic blood pressure, an increase in ejection fraction, and improved functional status. However, a retrospective study by Stack et al using data from the Center for Medicare and Medicaid Services found that new end-stage renal disease patients with a history of HF experienced poorer survival when treated with PD compared with hemodialysis. This and other studies that compare hemodialysis and PD results need to be interpreted cautiously because these investigations are subject to selection bias, may not have the appropriate control group, and often are retrospective in design. Clearly, a large-scale randomized trial is needed to evaluate the efficacy and safety of PD in the setting of chronic stable diuretic-resistant HF.

Therapeutic Effects Beyond Fluid Removal

Although current therapeutic options discussed in this review for HF (pharmacological and nonpharmacological) are mainly aimed at removal of excess water and sodium in these patients, it has been suggested that nonpharmacological modalities (ie, ultrafiltration and PD) might also have other beneficial effects beyond fluid volume removal. Indeed, one of the potential benefits of these therapies might be a reflection of avoiding adverse renal effects of high-dose diuretics, namely, increased RAAS stimulation and activation of SNS. It has been shown that in cirrhotic patients with increased SNS activity, similar to HF patients, the addition of clonidine, a centrally acting sympatholytic agent, decreases diuretic dose requirements and enhances diuretic responsiveness. Ultrafiltration has also been suggested to partially reverse the pathophysiological process of HF by removal of inflammatory cytokines and readjustment of neurohormonal pathways, with subsequent restoration of responsiveness to diuretics (see below). In addition, some authors have stressed the benefits of cytokine removal compared with the simple removal of fluid. In a recent study by Libetta et al on 10 patients with decompensated heart failure, the authors found a reduction in circulating proinflammatory cytokines (interleukin-8 and monocyte chemotactic protein-1) only in patients treated by intermittent hemodiafiltration compared with intravenous diuretic therapy alone. The authors concluded that intermittent hemodiafiltration is effective in removal of proinflammatory cytokines and might therefore improve myocardial
function and chronic vascular inflammation. We have previously described the shortcomings of this study. Overall, the mass clearance of these compounds is low; they have short half-life periods and can rapidly reappear in the plasma. Convective clearance is nonspecific in that beneficial cytokines are lost along with the potentially harmful ones, with no change in the source of inflammatory process. In regard to PD, the molecular weight of myocardial depressant factors ranges between 0.5 and 20 to 30 kDa. The ANP chain is composed of 17 to 28 amino acids, and the molecular weight of tumor necrosis factor-α is ≈ 17 kDa. It has been shown that ANP and tumor necrosis factor-α have transperitoneal clearance. It seems likely that myocardial depressant factors are also removed by PD, but this remains to be proven.

On the basis of these data, although it seems plausible that extracorporeal ultrafiltration and PD play a therapeutic role in HF beyond their removal of extracellular fluid, future studies are clearly needed to further investigate this issue.

**Optimal Hemoglobin Target**

Outside the scope of this review are various other diagnostic and therapeutic considerations typically in the purview of nephrology consultation. These include issues of renal artery stenosis inducing either kidney hypoperfusion or episodes of “flash” pulmonary edema, progression of underlying CKD, changes in vascular and tissue oncotic pressures due to protein-losing nephropathies, drug metabolism, and pharmacological approaches to minimize the cardiorenal syndrome. Anemia management, however, is of cardinal importance and is a topic that has merited special attention in the fields of both nephrology and cardiology.

Anemia is prevalent in both HF and CKD and is associated with worse outcomes in both diseases. Unlike most other comorbidities (eg, diabetes mellitus, hypertension, and obesity), management strategies for correction of anemia are quite divergent between CKD and HF. Although anemia is known to be associated with increased mortality and morbidity in HF patients, studies that focus on correction of anemia in these patients have reported contradictory results. Some authors have found that correction of anemia with erythropoietin improves functional capacity, quality of life, exercise tolerance, and renal function. However, a recent randomized, double-blind, placebo-controlled study failed to show any significant change in exercise tolerance, functional status, plasma BNP levels, or hospitalization rate. On the other hand, in patients with CKD, no major randomized controlled trial has thus far shown a significant reduction in cardiovascular events or death by targeting a hemoglobin level of >12 g/dL. In fact, a randomized trial in dialysis patients was stopped early after an interim analysis because of a significantly higher mortality rate in the group with a normal target hemoglobin level (14 g/dL). Furthermore, 2 randomized controlled trials recently confirmed that CKD patients with lower hemoglobin levels present a lower mortality rate. On the basis of currently available data, a target hemoglobin level of 10 to 12 g/dL for CKD patients has been recommended by the US Food and Drug Administration.

Because HF and CKD coexist in a great number of patients, studies on anemia correction in CKD patients have inevitably included patients with HF. However, no randomized clinical trial has specifically addressed the optimal hemoglobin level in CKD patients with HF. Therefore, the optimal hemoglobin levels in HF patients with CKD are not known, and it seems prudent, for now, to treat these patients in a manner similar to that used in the general CKD population and to avoid complete correction of anemia.

**Conclusion**

In summary, studies of new pharmacological agents for the management of refractory HF have thus far been associated with either limited or controversial results. Further large randomized controlled trials are clearly needed before these agents can be recommended for routine use in these patients. In the meantime, extracorporeal ultrafiltration could be employed cautiously as an adjunct therapy only in highly selected and hemodynamically stable patients when other less invasive options have been ineffective. Although the proposed superiority of fluid removal by extracorporeal devices has a potential physiological basis, close follow-up for potential adverse effects, including worsening kidney function, is warranted in these patients. Although available data are insufficient, PD shows a theoretical and practical potential in this setting. The extensive experience and literature in nephrology can be helpful in developing a risk-to-benefit analysis and strategy for implementing these ultrafiltration methods because they are associated with potential adverse effects.

**Disclosures**

None.

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Kazory and Ross

Nephrology-Oriented Management of CHF


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