Heart failure is a major and growing health problem. Major advances leading to newer therapies are being made in understanding the pathophysiology of heart failure as a chronic progressive disorder. Whatever the cause, all heart failure patients eventually progress to a refractory stage characterized by worsening renal function and resistance to diuretic therapy with attending severe edema. A logical treatment for this “cardiorenal syndrome” is the use of dialysis, which is efficient in treating both the hypervolemia and azotemia of refractory heart failure. Although all modalities of dialysis have been tried, peritoneal dialysis (PD) is the simplest choice and offers several advantages. It is an already-established long-term home-based therapy and does not require complex machinery or hospital resources. It is associated with preservation of residual renal function, gentle continuous ultrafiltration, hemodynamic stability, better middle-molecule clearance, sodium sieving with maintenance of normonatremia and perhaps less inflammation than hemodialysis is, especially with newer PD solutions. In the present paper, we discuss the potential advantages of PD in the treatment of heart failure, review the available literature, and lay some foundations for future research.

Key words
Heart failure, congestive heart failure, CAPD

Introduction
Heart failure is a major and growing public health problem in the United States. The overall incidence of congestive heart failure (CHF) approaches 10 per 1000 population after the age of 65 (1) and increases with increasing population age. The disorder is the primary reason for 12 – 15 million office visits and 6.5 million hospital days each year. In 2005 alone, the cost of heart failure management in the United States was $27.9 billion (2).

Although multiple clinical trials completed during the past 15 years have unequivocally shown a substantial reduction in mortality for patients with systolic heart failure, large epidemiologic surveys, such as the ongoing Framingham Study, have not documented any meaningful change in the overall death rate. Of people under 65 years of age who have CHF, 80% of the men and 70% of the women will die within 8 years (2). These statistics contrast with an average life expectancy of 16.3 years for men at age 65 and 19.2 years for women (3). During 1992 – 2002, deaths from heart failure increased by 35.3%, while during the same period, the overall death rate increased by 7.7% (2). This increase occurred despite advances in treatment in part because the number of heart failure patients is increasing. And that increase in the number of patients is the result of better treatment, “salvage” of patients with acute myocardial infarction (MI) earlier in life, and an overall increase in the elderly population.

Definition and classification of heart failure
The clinical syndrome of heart failure is the final pathway for myriad diseases that affect the heart. The traditional view—that heart failure is a constellation of signs and symptoms caused by inadequate performance of the heart—has changed since the 1980s. Currently, a complex blend of structural, functional, and biologic alterations are evoked to account for the progressive nature of heart failure and to explain the efficacy or failure of therapies used in clinical trials.

In keeping with the shift in the understanding of heart failure, the American Heart Association established a new classification of heart failure in its 2001 guidelines (4). The 2001 document identified four stages:

- In stage A, patients are at risk without structural change.
- In stage B, patients have structural heart disease, but without past or present symptoms and signs of heart failure.
- In stage C, patients have symptoms and signs of heart failure.
- In stage D, patients have refractory heart failure.
For diagnostic or coding purposes, only the stages C and D qualify for the traditional clinical diagnosis of heart failure.

This new classification system complements, but does not replace, the New York Heart Association (NYHA) functional classification, which gauges the severity of symptoms primarily in patients who are in stage C or D. The new staging highlights certain important factors in understanding heart failure:

- Heart failure is a culmination of various disorders affecting the endocardium, myocardium, pericardium, and the great vessels.
- Heart failure has common pathogenesis beyond a stage in the disease.
- A decrease in ejection fraction is not necessary for a diagnosis of heart failure.
- Heart failure is a progressive disorder.
- Treatment should be tailored to the stage of disease rather than to the patient’s symptomatology or NYHA class.

Pathophysiology of heart failure

Various conceptual paradigms have been put forward to explain the clinical syndrome of heart failure. The mechanistic view of heart failure as failure to pump blood at a rate required by the metabolizing tissues or the ability to do so only with elevated pressure is only partly correct. Research over the past few decades has highlighted the importance of neurohumoral mechanisms, the immune system, ventricular remodeling, and development of renal changes—that is, the “cardiorenal syndrome”—in the progression of disease. Details of the syndrome are beyond the scope of this review, but the salient features are these (5,6):

- Heart failure is a systemic, dynamic, progressive disease process brought on by interaction between the heart, kidneys, renin–angiotensin system, sympathetic nervous system, endothelium, and immune system through intricate feedback loops.
- Cardiorenal syndrome—the spiral of worsening heart failure and kidney failure that leads to diuretic resistance, volume overload, and refractory heart failure—develops.
- Apart from contributing to symptomatology, volume overload plays a significant role in the pathophysiology of progressive heart failure.

Management of heart failure

Because of the foregoing insights into pathophysiologic mechanisms, treatment of heart failure changed in the late 1980s. Beta blockers and angiotensin converting-enzyme (ACE) inhibitors were introduced as first-line treatment, and experimental therapies such as anti–tumor necrosis factor (TNF) agent, anti-vasopressin, and natriuretic peptides started to be studied.

The details of all the therapies for heart failure are not within the scope of this paper; readers are advised to consult the 2005 guidelines from the American College of Cardiology (7). Here, we discuss only problems with the management of salt and water excretion in refractory heart failure, the newer drugs, and the place of peritoneal dialysis (PD).

SODIUM AND FLUID BALANCE

The importance of salt and water management is illustrated by the fact that 80% of CHF hospitalizations are for acute decompensation. Most of these patients are admitted for fluid overload and congestion rather than for low perfusion. Only 5% of patients have low output at admission (8). Unfortunately, diuretic-based strategies are not always effective in reducing edema. In the Acute Decompensated Heart Failure National Registry, 21% of patients admitted for decompensated heart failure were discharged either without weight loss or with a gain in weight (9).

Salt and water excretion are impaired early in patients with CHF for these reasons:

- Low cardiac output leads to underfilling and a compensatory increase in sodium and water retention in proximal tubules.
- Activation of the renin–angiotensin–aldosterone system (RAAS) causes sodium retention mediated by angiotensin II through its action on the angiotensin I receptor.
- Release of aldosterone because of RAAS activation impairs distal tubular sodium excretion.
- Sympathetic activation leads to sodium and water retention indirectly by activating the RAAS system and by reducing the glomerular filtration rate (GFR) secondary to vasoconstriction.
- Impairment of GFR, mediated by various neurohormonal pathways and vasoactive molecules, impairs sodium and water excretion.
- Activation of vasopressin impairs water excretion.
Moreover, heart failure patients with mild-to-moderate disease have a response that is only one fourth to one third of that normally observed with maximally effective doses of loop diuretics. The response in patients with more severe disease is smaller yet (10). This situation is the result of many of the factors just described that cause salt and water retention, and not just from impaired absorption of oral drugs because of gastric congestion and from increased proximal tubular absorption with decreased delivery of filtrate to the ascending loop of Henle and the distal tubule, where traditional diuretics act.

Apart from failure of therapy, increased mortality with use of some classes of diuretics is a concern. The Studies of Left Ventricular Dysfunction database demonstrated that, compared with patients taking no diuretics, patients taking non-potassium-sparing diuretics alone had a significantly increased risk of hospitalization or death attributable to worsening heart failure (risk ratio: 1.31; 95% confidence interval: 1.09 to 1.57; \( p < 0.0004 \)). This increased risk was not observed in patients taking potassium-sparing diuretics with or without a non-potassium-sparing diuretic (11). Hence, the ongoing search for newer agents in the management of salt and water retention.

Many of the current standard therapies for heart failure directly or indirectly influence sodium and water excretion: beta blockers, ACE inhibitors, inotropes, and aldosterone antagonists. Newer agents such as vasopressin receptor antagonists (“vaptans”), natriuretic peptides, and adenosine receptor antagonists being developed for the treatment of heart failure also promote salt and water excretion. Among these, the vaptans are the only drugs that are close to being used in routine clinical practice.

**VASOPRESSIN RECEPTOR ANTAGONISTS**

Development of vasopressin receptor antagonists was prompted by the realization that levels of arginine vasopressin are elevated in heart failure and are believed to result in myocardial hypertrophy and vasoconstriction mediated by its action on vasopressin 1a receptor (causing vasoconstriction and increasing afterload) and water retention and hyponatremia mediated by its action on vasopressin 2 receptor (increasing preload). Early trials have shown that therapy with vaptans significantly reduces weight, corrects hyponatremia (12), and reduces mortality (13). These encouraging findings led to a large multicenter randomized double-blind trial called EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan), preliminary results of which were expected to be available in late 2006 (14).

**ULTRAFILTRATION**

Use of ultrafiltration for CHF was reported as early as in 1979 (15). But the need for bulky hemodialysis machines and central venous access made this treatment unpopular. Availability of a new peripheral venovenous hemofiltration machine (System 100: CHF Solutions, Brooklyn Park, MN, U.S.A.) has brought this treatment in focus again.

Most studies have demonstrated adequate fluid removal (average ultrafiltration volume) and relief of signs and symptom in the short term without causing hypotension (16–18). In the UNLOAD trial, the 90-day rehospitalization rate decreased (17). Marenzi et al. (19) demonstrated that mean right atrial, pulmonary artery, and wedge pressures decreased and that cardiac output and stroke volume increased during the procedure, and that all changes persisted up to 24 hours after procedure. But the studies demonstrated no actual change in patient weight (16), an increased requirement for diuretics after treatment (18), catheter-related infection (16), and anemia, probably because of procedural blood loss (16). Surprisingly, as compared with standard diuretic therapy, hemofiltration showed no difference in the incidence of renal failure (17,18).

Recently Gura et al. (20) reported development and animal trials of a new, wearable continuous ultrafiltering device. The device, which weighs slightly more than a kilogram, consists of a hollow-fiber filter, a 9-V battery–operated pulsatile blood pump, a micropump for heparin infusion, and another micropump to control the ultrafiltration rate. The blood flow used was 65 mL/min, and fluid removal rate ranged from 0 mL/h to 700 mL/h, averaging 106 mL/h.

This treatment modality is still in its infancy. Many questions remain unanswered, for example: Are there mortality and morbidity benefits? Which patients are likely to benefit and at what cost? Are the benefits sustained? Does treatment alter the cardiorenal syndrome or worsen it? Does treatment alter the pathophysiology of heart failure?
PERITONEAL DIALYSIS
In refractory heart failure, the predominant pathophysiology is sodium and fluid retention, and azotemia from renal hypoperfusion with inadequate response to traditional medical therapy. A logical treatment is dialysis, which is efficient in treating both the hypervolemia and azotemia of refractory heart failure.

Although all modalities of dialysis have been tried, PD is the simplest choice, offering several advantages. This home-based, long-term therapy is already well-established, and it does not require complex machinery or hospital resources. As compared with hemodialysis, PD is associated with preservation of residual renal function, gentle continuous ultrafiltration, hemodynamic stability, better middle-molecule clearance, sodium sieving with maintenance of normonatremia, and perhaps less inflammation—especially with the newer PD solutions.

Clearance of middle molecules could be important. Many cytokines and humoral factors have been implicated in the progression of heart failure. Many of these cytokines—for example, interleukin-1 and TNF—also are known to have a myocardial depressant effect. The molecular weights of these substances range between 500 Da and 30000 Da, which means that they are removable by PD. Zemel et al. (21) showed the appearance of TNFα and soluble TNF receptor 1 and 2 in PD effluent.

Hyponatremia is a marker for poor outcome in heart failure. Among heart failure patients treated with ACE inhibitors, diuretics, and beta blockers, even a small decline in serum sodium levels to 136 mEq/L or less as compared with levels greater than 136 mEq/L was associated with more than twice the risk of 60-day mortality and a significant increase in risk of readmission or death within 60 days (22). In a study of patients with end-stage heart failure, Licata et al. (23) attempted to isolate the effect of an increase in serum sodium on clinical outcome. They randomized 107 patients with refractory heart failure to receive an intravenous (IV) infusion of furosemide plus hypertonic 3% saline solution or an IV bolus of furosemide twice daily without hypertonic saline. Survival over a mean follow-up of 31 months was 55% in the group that received hypertonic saline as compared with 13% in those that did not receive hypertonic saline (p < 0.001). This finding suggests that normalization of low serum sodium by sodium sieving may be another potential benefit of PD for these patients.

Renal insufficiency significantly increases the risk of death and thus is an important prognostic indicator in heart failure patients. Hillege et al. (24) reported in the Second Prospective Randomized Study of Ilopanmine on Mortality and Efficacy that patients with a GFR in the lowest quartile (<44 mL/min) had a risk of mortality that was almost three times higher than that of patients in the highest quartile (>76 mL/min; relative risk: 2.85; p < 0.0001). In these patients with heart failure, impaired renal function was a stronger predictor of death than was low ejection fraction. Forman et al. (25) found that heart failure patients whose renal function worsened while in hospital experienced longer stays, incurred higher hospital costs, and were more likely to die in the hospital. If they survived the hospitalization, they were more likely to be readmitted. It is not clear whether this association occurs because patients with renal failure are more likely to have refractory heart failure or because preservation of renal function protects from worsening heart failure because of less inflammatory activation. Again, PD has the advantage by preserving residual renal function.

In 1949, Schneierson (26) published the first case report using PD as successful therapy in a patient with severe CHF. That report was followed by multiple case reports and small series. Review of PD use in CHF can be divided into three periods: intermittent PD, continuous PD, and newer solutions. During these three phases, the technology of PD not only changed, but treatment of CHF was also altered.

**Intermittent PD:** In the 1960s, many cases of acute CHF treated by PD were reported—about 56 in total. Briefly, these reports demonstrated a fluid removal rate of 67 – 568 mL/h with improvement in symptoms in most of the patients. Fluid removal was associated with an improvement in plasma volume (27) and hyponatremia (28), but the effect on cardiac output was variable. Interestingly, a significant proportion of patients became responsive to diuretics, and their renal function improved. Shilo et al. (29) demonstrated significant improvement in GFR as measured by creatinine and inulin clearance and also in renal blood flow as measured by para-aminohippurate clearance in 9 patients with refractory CHF who underwent intermittent PD. But, because of the acute and intermittent nature of the treatment, no change in the long-term course of the disease was observed.
Patients with remediable disease such as acute MI or those who underwent cardiac surgery benefited from the ultrafiltration. Raja et al. (30) first reported the use of repeated intermittent PD in a 59-year-old patient with refractory CHF. That patient underwent a total of 8 treatments over a period of 2 years and eventually died in a car accident. But later reports were not so optimistic. Shapira et al. (31) reported repeated intermittent PD in 10 patients with refractory CHF. Although all patients showed improvement in symptomatology, sodium levels, urine output, and diuretic responsiveness, 50% died 99 – 354 days after first dialysis. Among these patients, 90% also had gram-negative bacteria cultured from their PD fluid even though none developed peritonitis. A major limitation of the therapy was the requirement for frequent hospitalization for the procedure.

**Continuous ambulatory PD:** Despite the initial disappointment with intermittent PD in the long-term management of heart failure, it was clear that continuous ambulatory PD (CAPD) could be more appropriate. Multiple case series on the use of CAPD are available, and Table I summarizes the major trials. As can be seen in the table, all patients show symptomatic improvement while on PD. The hospitalization rate declined in all studies, except the one reported by Rubin and Ball (35). In that study, patients were hospitalized as often for PD-related problems as for cardiac problems. Peritonitis rates were high in the early studies, a problem that is less common with newer connectology and automated devices.

Although all patients showed symptomatic improvement, mortality remained high. Also, whether better volume management was translating into delay in the progression of heart failure was unclear. No correlation has been observed between functional improvement and left ventricular function as measured by left ventricular ejection fraction (33). But Stegmayr et al. (37) showed a reduction in left ventricular index by computed tomography, and Gotloib et al. (41) found an improvement in cardiac work index. Long-term follow-up studies are required to determine the effect on progression.

Mortality was high in most of those studies, but survival seems to be improving in recent trials. Stegmayr et al. (37) studied patients with an expected life survival of 1 month and showed significantly prolonged survival of up to 1 year. In the study by Gotloib et al. (41), the 1-year mortality rate was 10%, which was significantly less than the 80% expected based on the Charlson comorbidity scores of the patients.

These mortality data are difficult to interpret because none of the trials compared PD with standard care (or, for that matter, with cardiac transplantation), but a trial of that kind will not be possible in patients with refractory heart failure. Determining whether the improvements are the result of PD or of overall improved management in CHF patients with newer therapies is similarly difficult.

Interestingly, in the trial by Ryckelynck et al. (38), 2 patients who were earlier rejected for cardiac transplant were subsequently found to be fit after starting PD and were transplanted. In the trial by Konig et al. (36), 3 patients received cardiac grafts after starting PD. For patients awaiting cardiac transplant, PD could be offered as bridge therapy.

**Newer PD solutions:** Even in renal-failure patients on PD, the introduction of icodextrin has been shown to reduce extracellular water and to improve hemodynamics. Icodextrin offers several advantages:

- More physiologic ultrafiltration
- Maintenance of euvolemia without additional dextrose exchanges
- Lifestyle advantages and reduced risk of touch contamination (and hence of peritonitis) with a single daily exchange
- Possibly less peritoneal inflammation because of avoidance of dextrose solutions (The effect of inflammatory markers on progression of heart disease is not known.)

Konings et al. (43) randomized 40 CAPD or continuous cycling PD patients (renal failure patients on dialysis) to either icodextrin or standard glucose solution during the long dwell. These authors found that use of icodextrin was associated with increased ultrafiltration and reduced extracellular water as estimated by the bromide dilution method. At the end of a 4-month follow-up period, the patients were also found to have significantly lower left ventricular mass.

Only a few case reports describe the use of icodextrin in the treatment of refractory CHF. Bertoli et al. (44) reported use of single 12-hour nighttime manual CAPD exchange with icodextrin in 2 non
uremic elderly patients with NYHA class 3 – 4 heart failure. These patients experienced daily ultrafiltration of 500 – 1000 mL. Both patients showed improvement in their NYHA class and ejection fraction after 12 – 15 months on PD. Urine output declined modestly in 1 patient, but renal function measured as creatinine clearance by the Cockcroft–Gault method improved in both patients. Neither patient required hospitalization for either cardiac or dialysis problems, as compared with multiple admissions in the preceding year.

Future prospects

- Studies are needed to compare PD with standard therapy and with ultrafiltration devices to demonstrate relative survival benefits, morbidity, and costs.
- As compared with standard medical therapy, does PD preserve renal function? Does PD treatment delay the progression of heart failure by interrupting cardiorenal syndrome?
- What is the effect of biocompatible PD solution, with associated lesser inflammation, on the pathogenesis of heart failure?
- Large trials with long-term follow-up are needed to look at the effect of PD on the progression of heart failure.

References

4. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of


17 Cleland JG, Coletta AP, Nikitin NP, Clark AL. Clinical trials update from the American College of Cardiology: darbepoetin alfa, ASTEROID, UNIVERSE, paediatric carvedilol, UNLOAD and ICELAND. Eur J Heart Fail 2006;8:326–9.


**Corresponding author:**

Dimitrios G. Oreopoulos, MD PhD FRCP FACP, Professor of Medicine, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario M5T 2S8 Canada.

**E-mail:**
dgo@teleglobal.ca