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Ultrafiltration in Acute Decompensated Heart Failure

By WAIL ALKASHKARI, MD, and GORDON MOE, MD

Acute heart failure is a major clinical and public health problem. Advanced refractory heart failure represents an important subgroup of patients presenting with acute heart failure syndrome. Fluid congestion is a hallmark in patients with advanced heart failure, and resistance to pharmacologic therapy – particularly diuretics – frequently develops as the disease progresses. When pharmacologic therapy is no longer feasible, ultrafiltration, dialysis, or phlebotomy may permit fluid removal. The role of ultrafiltration in the management of patients with acute decompensated heart failure is discussed in this issue of *Cardiology Rounds*.

Recent data from large registries and clinical trials have clearly identified fluid overload and pulmonary congestion as the main reasons for hospitalization in the great majority of patients with acute decompensated heart failure (HF).[1-5] The potential detrimental consequences of pulmonary congestion and elevated ventricular filling pressure are also well known[4] and include:

- induction of myocardial ischemia
- cell death by necrosis or apoptosis secondary to increased wall stress and decreased coronary perfusion
- worsening of mitral and tricuspid regurgitation due to chamber dilation and spherical remodeling of the ventricles
- impairment of ventricular systolic and diastolic functions.

Relief of circulatory congestion overload has been shown to have a favourable effect on symptoms and length of hospital stay, rate of rehospitalization, and long-term survival.[6,7] Therefore, this should be the goal of therapy in these patients.

Intravenous loop diuretics have been the mainstay of therapy for fluid overload and are used in the great majority of patients with decompensated HF.[5] Although these drugs can achieve effective diuresis in the majority of patients, their use in those with acute decompensated HF may be limited because of adverse effects such as electrolyte abnormalities, neurohormonal stimulation, and worsening renal function.[1,8] In addition, it is common for patients with advanced HF to become refractory to diuretics and, therefore, achieving effective diuresis often requires aggressive strategies, including the use of loop diuretics either in high doses or in combination with other types of diuretics. High-dose diuretics, however, have been associated with worsening renal function, prolongation of hospital length of stay, and increased mortality.[9,10] Intravenous vasodilators rapidly improve resting hemodynamics and reduce ventricular filling pressures and myocardial oxygen consumption.

Vasodilators can also decrease systemic vascular resistance, decrease ventricular workload, increase stroke volume, and improve cardiac output.[11] Nitroglycerin (NTG) is the

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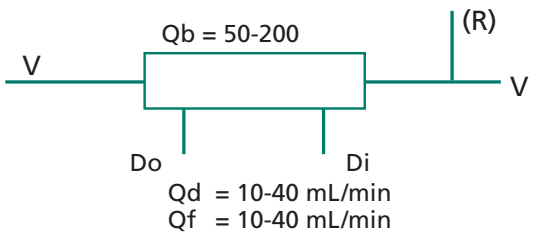
Figure 1: Scheme for veno-venous ultrafiltration



Qb = blood flow, Qd = dialysate flow, Qf = UF rate, Do = dialysate outlet, Di = dialysate inlet, R = replacement fluid, V = veins

vasodilator that is commonly used to relieve congestion. While it is an effective vasodilator, frequent dose titration of IV NTG is often necessary to produce the desired hemodynamic effects and symptomatic relief and high doses may be necessary to sufficiently decrease filling pressures and alleviate symptoms.[12] Furthermore, the effect of NTG on urine output in patients with decompensated HF has not been evaluated.

The effect of nesiritide, a recombinant human B-type natriuretic peptide, has been studied more extensively than NTG. Most studies, however, have been limited to small numbers of patients and results have been conflicting.[13,14] Inotropes are frequently used in patients with acute decompensated HF with low systemic pressures. However, these agents are not effective in relieving congestion.[15] The use of dobutamine is supported by small studies documenting improved hemodynamics.[16] The only randomized controlled study of adequate sample size – the Outcome of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-HF) – examined milrinone in 951 patients with decompensated HF, but with preserved systolic blood pressure.[17] The use of milrinone was associated with an excess of adverse events driven by increased systemic hypotension and atrial fibrillation.

Peripheral ultrafiltration

Extracorporal ultrafiltration (UF) is a mechanical strategy that uses the convection-driven movement of water and nonprotein-bound small-to-medium molecular weight solutes across a semi-permeable membrane to reduce volume overload. Convection allows for fluid removal solvent drag, ie, solute is removed passively by accompanying the solvent flow (Figure 1).[18] Because both water and electrolytes are simultaneously moved across the membrane, the electrolyte concentration of the ultrafiltrate is similar to that of overall blood-plasma. This avoids sudden shifts in electrolyte concentrations and results in more sodium removal than would be achieved with the use of diuretics.

Figure 2: An ultrafiltration console

However, conventional veno-venous UF has a few potential limitations. It requires physician placement of a double-lumen central venous catheter and monitoring by a dedicated dialysis technician. Recently, new, more simplified UF devices have been introduced that allow placement of blood withdrawal and infusion catheters in peripheral arm veins by nonphysician personnel and monitoring by a trained clinical nurse. Software features also permit automated resolution of common pump-related problems with minimal operator intervention.

A typical set-up consists of a dual rotary occlusive pump device that is used with a sterile single-use blood circuit set (Figure 2). This disposable set consists of a hemofilter, withdrawal and infusion blood tubing, withdrawal and infusion ultrafiltrate pressure sensor, and 2 venous catheters. Ultrafiltration catheters can be placed by trained intravenous team members. Blood is withdrawn from a peripheral arm vein (eg, the antecubital vein proximal to the shoulder) using a 16 gauge, 25 or 35 cm, soft material. A 16 or 18 gauge, 3.5 cm catheter is used for blood return via a second peripheral vein (typically in the forearm). Software algorithms adjust the withdrawal and infusion blood flows and pressure.

Ultrafiltration in heart failure

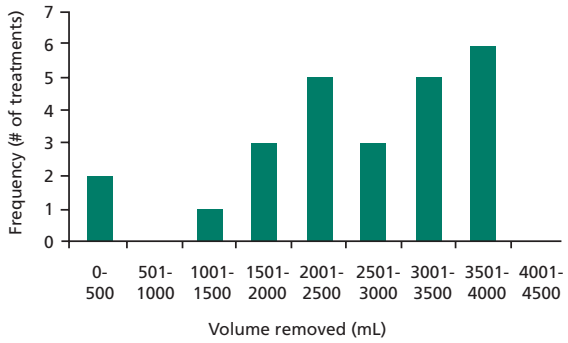
Rimondini et al were among the first groups to examine the effect of UF in 11 patients with heart failure and New York Heart Association (NYHA) class IV symptoms refractory to medical treatment.[19] Fluid was removed from plasma at a rate of 500 ml/hour until either normalization of the right atrial pressure was achieved or the hematocrit value exceeded 50%. Based on these criteria, the duration of treatment ranged from

4-6 hours and the total amount of fluid removed was 2,000 to 3,000 ml. In each case, UF was found to relieve dyspnea, clinical and radiographic evidence of lung congestion and pleural effusion, and substantially reduce dependent edema and abdominal girth. These effects occurred in parallel to a progressive decrease in right- and left-sided filling pressures and in pulmonary arterial pressure and arteriolar resistance, without significant variations in heart rate, aortic pressure, cardiac index, and systemic vascular resistance. Urinary output was substantially enhanced by the procedure. The study indicated that UF might be a short-term treatment for refractory heart failure with fluid overload and that a filtration rate of 500 mL/hour might be safe and effective.

Ramos et al performed UF on 30 patients also with NYHA class IV symptoms refractory to therapy.[20] Using retrospectively defined clinical outcomes, they found that younger age groups, greater fluid removal, as well as significant decreases in blood urea nitrogen, serum creatinine, and right atrial and pulmonary wedge pressures after UF, are associated with favourable outcome. Conversely, older age groups, less fluid removal, and rising blood urea nitrogen and serum creatinine levels after UF were associated with poor outcome. The hemodynamic and circulatory adjustments to UF in refractory HF were examined in 24 patients.[21] Hemodynamics, blood gas analysis, plasma volume changes, and plasma refilling rate were measured after every liter of plasma water was removed. In all patients, UF was completed without hemodynamic instability (ultrafiltrate = 4,880±896 ml). Mean right atrial, pulmonary artery, and wedge pressures progressively reduced during the procedure. Cardiac output increased at the end of the procedure and, to a greater extent, 24 hours later, in relation to the increase in stroke volume. Heart rate and systemic vascular resistance did not increase and other peripheral biochemical parameters did not worsen during UF. Intravascular volume remained stable throughout the entire duration of the procedure, indicating that a proportional volume of fluid was refilled from the congested parenchyma.

A more simplified peripheral UF system, including a miniaturized disposable circuit, was evaluated prospectively in 21 patients with volume-overload states.[22] Separate intravenous catheters (16-18 gauge) for the withdrawal and return of blood (blood flow ≤40 mL/min, ultrafiltrate ≤500 ml/h) were placed by nonphysician personnel in the upper extremity veins. Twenty-five treatments of up to 8 hours were performed in 21 patients. The primary endpoint of >1 litre of fluid removal in <8 hours was achieved in 23 of 25 treatments. The distribution of fluid volume removed in 25 treatments of ultrafiltration is shown on Figure 3. On average, 2611±1002 ml (maximum 3,725 ml) of ultrafiltrate was removed per treatment (treatment period 6:43±1:47 hr:min). Patient weight decreased from 91.9±17.5 to 89.3±17.3 kg ($p<0.0001$) after UF. There were no significant changes in heart rate and blood pressure and no major adverse events occurred. This study, therefore, demonstrated that rapid removal of extracellular and intravascular fluid volume excess can be safely achieved via peripherally-inserted UF without the need for central venous catheter placement.

Figure 3: Frequency versus fluid volume removal



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The Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure (RAPID-CHF) trial was the first randomized controlled trial that assessed the safety and efficacy of UF in patients admitted with decompensated HF.[23] Patients admitted for HF and with evidence of volume overload were randomized to a single, 8-hour, UF session using a simple UF device that did not require special monitoring or central intravenous access, in addition to usual care, or usual care alone. Fluid was removed via a 35 cm, 16-gauge catheter placed in the antecubital fossa at a rate of up to 500 ml/hr. The primary endpoint was weight loss 24 hours after the time of enrollment. Forty patients were enrolled (20 UF, 20 usual care). Ultrafiltration was successful in 18 of the 20 patients in the UF group. Fluid removal after 24 hours was 4,650 ml and 2,838 ml in the UF and usual care groups, respectively ($p<0.001$). Twenty percent of the patients had additional UF sessions at 24 to 48 hrs, resulting in additional 3.650-4.175 L of UF removal. Weight loss after 24 hours, the primary endpoint, was 2.5 kg and 1.9 kg in the UF and usual care groups, respectively ($p=0.240$). There were no significant differences in the change in global dyspnea symptoms at 24 and 48 hours. Patients tolerated UF well. This randomized controlled study demonstrated that the early application of UF for

patients with HF was feasible, well-tolerated, and resulted in significant fluid removal.

The Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial was a prospective, randomized, multi-centre trial of early UF versus intravenous diuretics in patients hospitalized with HF and hypervolemia.[24] Patients hospitalized for HF with >2 signs of hypervolemia (peripheral edema >2+; jugular venous distension >7 cm; radiographic pulmonary edema or pleural effusion; enlarged liver or ascites; or pulmonary rales, paroxysmal nocturnal dyspnea, or orthopnea) were randomized to UF or intravenous diuretics. By study design, there was no ejection fraction inclusion criterion. Patients were excluded for acute coronary syndrome, serum creatinine >3.0 mg/dL, systolic blood pressure <90 mm Hg, unattainable venous access, requirement for intravenous pressors, and vasoactive drug use. Primary endpoints were weight loss and dyspnea assessment at 48 hours after randomization. Secondary endpoints included net fluid loss at 48 hours functional capacity, HF rehospitalizations, and unscheduled visits in 90 days. Safety endpoints included changes in renal function, electrolytes, and blood pressure.

Two hundred patients (aged 63±15 years, 69% men, 71% having an ejection fraction of <40%) were randomized. At 48 hours, the primary endpoint, weight loss (5.0±3.1 kg vs. 3.1±3.5 kg; p<0.001) and net fluid loss (4.6 vs. 3.3 l; p<0.001) were greater in the UF group. Dyspnea scores were similar. Subgroup analyses revealed no heterogeneity in the effect of UF on 48-hour weight loss. Fewer patients in the UF group required vasoactive

Figure 4: Average serum Na for all 20 patients and for the 7 patients presenting with Na <135 mg/dL

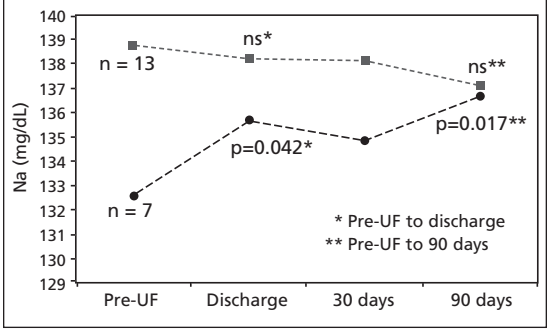

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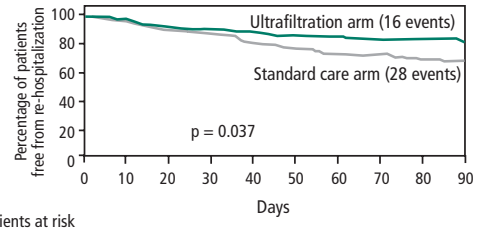
Figure 5: Effect of ultrafiltration on heart failure rehospitalization. Kaplan-Meier estimate of freedom from rehospitalization for heart failure within 90 days after discharge in the UF (green line) and standard care (black line) groups.



No. Patients at risk										
Ultrafiltration arm	88	85	80	77	75	72	70	66	64	45
Standard care arm	86	83	77	74	66	63	59	58	52	41

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drugs at 48 hours (3 of 96 [3.1%] vs. 12 of 99 [12%]; p=0.015). Serum sodium (Na) was 136±4 mg/dL (range 128 to 142 mg/dL) and remained unchanged. In 7 patients with serum Na <135 mg/dL, Na increased from pretreatment values at discharge (p=0.042) and at 90 days (p=0.017) (Figure 4).

At 90 days, the UF group had fewer:

- patients rehospitalized for HF (16 of 89 [18%] vs. 28 of 87 [32%]; p= 0.037),
- HF rehospitalizations (0.22±0.54 vs. 0.46±0.76; p=0.022) (Figure 5),
- rehospitalization days (1.4±4.2 vs. 3.8±8.5; p=0.022) per patient
- unscheduled visits (14 of 65 [21%] vs. 29 of 66 [44%]; p=0.009).

No serum creatinine differences occurred between groups. Nine deaths occurred in the UF group and 11 in the diuretics group. Results of this randomized controlled trial, therefore, demonstrate that early ultrafiltration safely produces greater weight and fluid loss than intravenous loop diuretics in hypervolemic HF patients. This benefit is translated into decreased rehospitalizations for HF and unscheduled medical visits.

Summary

Substantial gaps remain in both the understanding and treatment of acute HF. Intravenous loop diuretics currently form the foundation of care for patients with acute decompensated HF who have volume overload, but even diuretic use in acute HF remains controversial. Data to date suggest that UF is an attractive alternative therapy to diuretics. However, the mechanisms behind the

relative advantages and any potential cost benefits remain to be determined. The upfront cost of UF may be expensive, but it could possibly be defrayed by cost-savings down the road. Although UF is approved in the United States for the treatment of volume overload, whether it is appropriate for routine use in the general care of patients with acute decompensated HF in other healthcare systems, including that in Canada, remains to be determined.

Dr. Wail Alkashkari is a cardiology trainee at St Michael's Hospital.

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Abstracts of Interests

Early Ultrafiltration in Patients With Decompensated Heart Failure and Diuretic Resistance

COSTANZO MR, SALTZBERG M, O'SULLIVAN J, SOBOTKA P; LOMBARD, ILLINOIS; AND BROOKLYN PARK, MINNESOTA

OBJECTIVES: We sought to determine if ultrafiltration before intravenous (IV) diuretics in patients with decompensated heart failure and diuretic resistance results in euvolemia and early discharge without hypotension or worsening renal function.

BACKGROUND: Heart failure patients with renal insufficiency and diuretic resistance have increased hospital mortality and length of stay. Peripheral veno-venous ultrafiltration may re-establish euvolemia and diuretic responsiveness.

METHODS: Ultrafiltration was initiated within 4.7±3.5 h of hospitalization and before IV diuretics in 20 heart

failure patients with volume overload and diuretic resistance (age 74.5± 8.2 years; 75% ischemic disease; ejection fraction 31 ± 15%) and continued until euvolemia. Re-evaluation was each hospital day, at 30 days, and at 90 days.

RESULTS: A total of 8,654±4,205 mL were removed with ultrafiltration. Twelve patients (60%) were discharged in ≤3 days. One patient was readmitted in 30 days. Weight (p=0.006), Minnesota Living with Heart Failure scores (p=0.003), and Global Assessment (p= 0.00003) improved after ultrafiltration and at 30 and 90 days. Median B-type natriuretic peptide levels decreased after ultrafiltration (from 1,230 pg/mL to 788 pg/mL) and at 30 days (815 pg/mL) (p=0.035). Blood pressure, renal function, and medications were unchanged.

CONCLUSIONS: In heart failure patients with volume overload and diuretic resistance, ultrafiltration before IV diuretics effectively and safely decreases length of stay and readmissions. Clinical benefits persist at three months.

J Am Coll Cardiol 2005;46:2047-2051.

Peripherally Inserted Veno-Venous Ultrafiltration for Rapid Treatment of Volume Overloaded Patients

Jaski BE, Ha J, Denys BG, Lamba S, Trupp RJ, Abraham WT. San Diego, California; Thibodaux, Louisiana; Lexington, Kentucky

BACKGROUND: Veno-venous ultrafiltration may benefit patients with acute or chronic circulatory volume overload. Use of conventional systems, however, may be cumbersome, requiring physician placement of a double-lumen central venous catheter and use of a dedicated dialysis technician and apparatus.

METHODS: A simplified peripheral ultrafiltration system including a miniaturized disposable circuit was evaluated in patients with volume-overload states. Separate intravenous catheters (16-18 G) for withdrawal and return of blood (blood flow ≤40 mL/min, ultrafiltrate ≤500 mL/h) were placed by nonphysician personnel in upper extremity veins. Twenty-five treatments of up to 8 hours were performed in 21 patients.

RESULTS: The primary endpoint of greater than 1 L fluid removal in less than 8 hours was achieved in 23 of 25 treatments. On average, 2611±1002 mL (maximum 3,725 mL) of ultrafiltrate was removed per treatment (treatment period 6:43±1:47 hours:minutes). Patient weight decreased from 91.9±17.5 to 89.3±17.3 kg (P<.0001) after ultrafiltration. No major adverse events occurred.

CONCLUSIONS: Rapid removal of extracellular and intravascular fluid volume excess can be safely achieved via peripherally inserted ultrafiltration without the need for central venous catheter placement.

J Card Fail 2003; 9(3):227-231.

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