Ultrafiltration in the Management of Heart Failure

a report by

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In the US, 90% of the one million annual hospitalizations for heart failure (HF) are due to volume overload. Hypervolemia contributes to HF progression and mortality. Guidelines recommend that therapy for HF patients be aimed at achieving euvolemia. Intravenous loop diuretics induce rapid diuresis that reduces lung congestion and dyspnea. However, the effectiveness of loop diuretics declines with repeated exposure. Unresolved congestion may contribute to high re-hospitalization rates. Furthermore, loop diuretics may be associated with increased morbidity and mortality due to deleterious effects on neurohormonal activation, electrolyte balance, and cardiac and renal function. Ultrafiltration is an alternative method of sodium and water removal that safely improves hemodynamics in HF patients. The application of this technology has been limited by the need for high flow rates, large extracorporeal blood volumes, and large-bore central venous catheters. A modified ultrafiltration device has overcome these limitations.

The Process

Ultrafiltration is the production of plasma water from whole blood across a semipermeable membrane (hemofilter) in response to a transmembrane pressure gradient generated by the hydrostatic pressures in the blood and in the filtrate compartments and the oncotic pressure produced by plasma proteins. Hydrostatic pressure is determined by the blood pressure in the filtering device, generated by either the patient’s blood pressure or an extracorporeal pump plus the suction occurring in the ultrafiltrate compartment. With isolated ultrafiltration, the solute is passively removed by accompanying the solvent flow (convective transport): the sodium concentration in the ultrafiltrate is equal to that in the water component of the plasma. After cannulation of an artery or vein, ultrafiltration is performed on blood extracted from and then returned to the patient via a separate access to the venous circulation. Ultrafiltration can be isolated, intermittent, or continuous. With appropriate ultrafiltration rates, the extracellular fluid gradually refills the intravascular space and blood volume is maintained. If the ultrafiltration rate is too high, blood volume may decrease because intravascular volume depletion exceeds reabsorption of fluid from the interstitium into the vascular space. Accurate determination of the amount of fluid to be removed, optimization of the fluid removal rate, and maintenance of circulating blood volume are critically important.

The fluid removed with diuretics is hypotonic. In contrast, the ultrafiltrate is essentially iso-osmotic and isonatric compared with plasma. Therefore, for any amount of fluid withdrawn, more sodium is removed with ultrafiltration than with diuretics. With diuretics, intravascular hypovolemia is prolonged and inhibition of sodium chloride uptake in the macula densa enhances renal renin secretion. In turn, the augmented neurohormonal activation promotes sodium and water retention, ultimately reducing the ability of diuretics to relieve circulatory congestion.

Ultrafiltration does not stimulate macula densa-mediated neurohormonal activation, and does not produce prolonged intravascular hypovolemia because it removes fluid from the blood at the same rate at which fluid is reabsorbed from the edematous interstitium.

The Use of Ultrafiltration in Heart Failure

Ultrafiltration improves congestion, lowers right atrial and pulmonary arterial wedge pressures, improves cardiac output, decreases neurohormone levels, corrects hyponatremia, restores diuresis, and reduces diuretic requirements.

The use of ultrafiltration in patients with moderate HF has shed light on the beneficial mechanisms of ultrafiltration. Sixteen patients with New York Heart Association (NYHA) class II and III HF were randomly allocated to receive either a single ultrafiltration treatment (n=8) or intravenous furosemide (n=8; mean dose 248mg) to remove 1,600ml of fluid. Soon after fluid withdrawal by either method, biventricular filling pressures and bodyweight were reduced and plasma renin, norepinephrine, and aldosterone levels were increased. After furosemide, neurohormones levels remained elevated over four days, and during this period patients had positive water balance, recurrent elevation of filling pressures, and lung congestion without an improvement in VO_{2max}. After ultrafiltration, neurohormone levels fell below baseline within 48 hours, whereas water metabolism was equilibrated at a new set point (less fluid intake and diuresis without weight gain). Improvement was sustained at three months after ultrafiltration. Although ultrafiltration and furosemide are equally effective in terms of acute volume of fluid removed and resolution of congestive symptoms, their long-term effects are different. The effects of ultrafiltration on pulmonary water metabolism and neurohormone levels may be due to mechanisms not occurring with diuretics. The ultrafiltrate has a different sodium content than the fluid.
removed with diuretics. Ultrafiltration removes fluid with a sodium concentration similar to that of plasma, so that approximately 150mmol of sodium are withdrawn with each liter of ultrafiltrate. In contrast, the urine of patients with heart failure is hypotonic compared with plasma and the 50mmol of sodium usually present in 1 liter of urine increases to only 100mmol with furosemide administration. The different amounts of sodium removed with similar amounts of fluid account for the differential effects of ultrafiltration and diuretics on neurohormonal responses, which in turn will result in differing renal sodium and water reabsorption.

Among 32 NYHA class II–IV hypervolemic HF patients, baseline 24-hour diuresis and natriuresis were inversely related with neurohormone levels and renal perfusion pressure. The response to ultrafiltration ranged from neurohormonal activation and reduction of diuresis in patients with the mildest hypovolemia and urine output greater than 1,000ml per 24 hours to neurohormonal inhibition and enhanced diuresis and natriuresis in those with the most severe volume overload and urine output less than 1,000ml per 24 hours. Decreases in norepinephrine levels were proportional to the enhancement of diuresis. Thus, subtraction of total body water uncovers enough cardiac reserve to increase cardiac output and attenuate neurohormonal activation. Benefits are then maintained because the enhanced diuresis improves norepinephrine clearance from the circulation. The earliest effect of ultrafiltration may be the reduction of the extravascular pulmonary fluid, with a subsequent decrease in pulmonary extravascular resistance, improvement of ventilation and gas exchange, and a decrease in hypoxia-induced vasconstriction. Ultrafiltration itself, via baroreceptor-mediated reflexes, may re-set neurohormonal activation, which may explain the intermediate- and long-term benefits of ultrafiltration. The removal of myocardial depressant factors may also occur. In 36 patients with acutely compensated HF, ultrafiltration was associated with increased cardiac index and oxygenation status, decreased pulmonary artery pressure and vascular resistance, and a reduced requirement for inotropes. It is unknown whether the clinical benefits of ultrafiltration translate into improved survival. In decompensated HF patients, ultrafiltration has been used predominantly after diuretics have failed or in the presence of acute renal failure. Earlier utilization of ultrafiltration can expedite and maintain the compensation of acute HF by improving. Plasma volume falls and oncotic pressure rises. Ultrafiltration treatment, suggesting that untapped cardiac functional reserve is unmasked. Many patients regain responsiveness to diuretics after one or more ultrafiltration treatments, suggesting that untapped cardiac functional reserve is recruited by ultrafiltration. Ascites, edema, dyspnea, and hyponatremia may improve. Plasma volume falls and oncotonic pressure rises. Ultrafiltration increases transcapillary gradient and plasma colloid osmotic pressure. This increase is maximal during the first 60 minutes of ultrafiltration and then levels decrease, indicating that fluid removal is occurring from the intravascular to the interstitium.
Heart Failure

off as refilling occurs. After ultrafiltration, the decreased venous pressure further enhances the net transcapillary pressure gradient change, favoring interstitial fluid reabsorption.

If the ultrafiltration rate is limited to 500–1,000ml/hour for only a few hours, heart rate, blood pressure, and systemic vascular resistance remain unchanged.14 Cardiac output either rises or remains stable. Pulmonary capillary wedge pressure is unchanged or decreased. Right atrial pressure and pulmonary vascular resistance fall. An improved ejection fraction and a decreased radiographic cardiothoracic ratio have also been described.10

Advantages of intermittent isolated ultrafiltration include the avoidance of an arterial puncture and the short exposure to systemic anticoagulation. Disadvantages include the need for dialysis equipment and personnel, and the removal of large amounts of fluid in a short time period. Hemorrhage from anticoagulation and extracorporeal blood pump complications, such as air embolism, can occur.

Intermittent isolated ultrafiltration has been described in more than 100 patients with NYHA class IV refractory HF.23 Of 52 patients treated with slow isolated ultrafiltration, 13 died in less than one month during treatment (non-responders), 24 experienced both cardiac and renal improvement (responders) for either less than three (n=6) or more than three months (n=18), and 15 (partial responders) had hemodynamic improvement but worsening renal function requiring either long-term weekly ultrafiltration (n=8), continuous ambulatory peritoneal dialysis (n=1), or intermittent renal replacement therapy (n=6). Adequate diuresis was restored within one month in 24 of the 39 responders and partial responders. Four of the 15 partial responders had sufficient recovery of renal function to undergo heart transplantation within three to nine months. Thus, intermittent ultrafiltration can be used to treat HF refractory to maximally tolerated medical therapy. Restoration of diuresis and natriuresis after intermittent ultrafiltration identified patients with recoverable cardiac functional reserve. Intermittent isolated ultrafiltration is valuable in partial responders because it improves quality of life and may be used as a bridge to heart transplantation. The high short-term mortality is consistent with the poor prognosis of advanced HF.

A new device, the Aquadex™ System 100 (CHF Solutions, Minneapolis), permits both the withdrawal of fluid and blood return through peripheral veins (see figure 1). However, central venous access remains an option. Fluid removal can range from 10 to 500ml/hour, blood flow can be set at 10–40ml/minute, and total extracorporeal blood volume is only 33ml. The device consists of a console, an extracorporeal blood pump, and venous catheters. The console controls blood removal rates and extracts ultrafilterate at a user-set maximum rate. The device is designed to monitor the extracorporeal blood circuit and to alert the user to abnormal conditions. Ultrafilterate drains into a bag. Blood is withdrawn from a vein through the withdrawal catheter. Tubing connects the withdrawal catheter to the blood pump. Blood passes through the withdrawal pressure sensor just before it enters the blood pump tubing loop. During operation, the pump loop is compressed by rotating rollers that propel the blood through the tubing. After exiting the blood pump, blood passes through the air detector and enters the hemofilter. The hemofilter is bonded to a clip-on cartridge that mounts onto the ultrafiltrate pump raceway on the side of the console. Blood enters the filter through a port on the bottom, exits through the port at the top of the filter, and passes through the infusion pressure sensor before returning to the patient. Inside the hemofilter there is a bundle of hollow fibers. The ultrafiltrate passes through the fiber walls, fills the space between these fibers, and exits through a port near the top of the filter case. Ultrafiltrate then passes through a blood-leak detector. Ultrafiltrate sequentially passes through the ultrafiltrate pressure sensor, ultrafiltrate pump, and collecting bag that is suspended from the weight scale. Treatment can be performed by any nurse trained in the use of the device.

The aim of the second study was to determine whether ultrafiltration with the Aquadex System 100 before intravenous diuretics in patients with decompensated HF and diuretic resistance resulted in euvoolemia and hospital discharge in three days without hypotension or worsening renal function. Ultrafiltration was initiated within 4.7±3.5 hours of hospitalization and before intravenous diuretics in 20 HF patients with volume overload and diuretic resistance (age 74.5±8.2 years; 75% ischemic disease; ejection fraction 3a15%), and continued until euvoolemia. An average of 8,654±4,205ml was removed with 2.6±1.2 eight-hour ultrafiltration courses (eight hours each). Twelve patients (60%) were discharged within three days. One patient was re-admitted within 30 days and two patients within 90 days for reasons unrelated to recurrent volume overload. Weight (p=0.006), Minnesota Living with Heart Failure scores (p=0.003), and global assessment (p=0.0003) were improved after ultrafiltration at 30 and 90 days. B-type natriuretic peptide levels were decreased after ultrafiltration (from 1,236±747 to 988±847pg/ml) and at 30 days (816±494pg/ml; p=0.03). Blood pressure, renal function, and medications were unchanged. Thus, in HF patients with volume overload and diuretic resistance, early ultrafiltration before intravenous diuretics effectively and safely decreases length of stay and re-admissions. Benefits persisted at three months after treatment.22

The aim of the third study was to compare the safety and efficacy of ultrafiltration using the Aquadex System 100 device with the efficacy and safety of intravenous diuretics in decompensated HF patients. Compared with the 20 diuretic-treated patients, the 20 patients randomized to a single eight-hour ultrafiltration session had greater median fluid removal (2,838 versus 4,650ml; p=0.001) and weight loss (1.86 versus 2.5kg; p=0.24). Ultrafiltration was well tolerated and not associated with adverse hemodynamic or renal effects. Thus, early ultrafiltration in decompensated HF patients results in greater fluid removal and improvement of congestion than those achieved with intravenous diuretics.23 The findings of these studies stimulated the design and implementation of the Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial.24 This study was designed to compare the safety and efficacy of veno–venous ultrafiltration with standard intravenous diuretic therapy for hospitalized HF patients with ≥2 signs of hypervolemia. Two hundred patients (mean age 63±15 years; 69% men; 71% ejection fraction ≤40%) were randomized to ultrafiltration or intravenous diuretics. At 48 hours, weight (5±3.1 versus 3.1±3.5kg; p=0.001) and net fluid loss (4.6 versus 3.3 liters; p=0.001) were greater in the ultrafiltration group. Dyspnea scores were similar. At 90 days, the ultrafiltration group had fewer patients rehospitalized for HF (16 of 89 [18%] versus 28 of 87 [32%]; p=0.037), HF rehospitalizations (0.22±0.54 versus 0.46±0.76; p=0.022), rehospitalization days (1.4±4.2 versus 3.8±8.5; p=0.022) per patient, and...
unscheduled visits (14 of 65 [21%] versus 29 of 66 [44%]; p=0.009). Changes in serum creatinine were similar in the two groups throughout the study. The percentage of patients with rises in serum creatinine levels >0.3mg/dl was similar in the ultrafiltration and standard care group at 24 hours (3/90 [14.4%] versus 7/91 [7.7%]; p=0.528), at 48 hours (18/88 [26.5%] versus 15/74 [20.3%]; p=0.430), and at discharge (19/84 [22.6%] versus 17/86 [19.8%]; p=0.709). There was no correlation between net fluid removed and changes in serum creatinine in the ultrafiltration (r=0.050; p=0.695) or in the intravenous diuretics group (r=0.028; p=0.820). No clinically significant changes in serum blood urea nitrogen, sodium, chloride, or bicarbonate occurred in either group. Serum potassium <3.5mEq/l occurred in 1/77 patients (1%) in the ultrafiltration and in 9/75 patients (12%) in the diuretics group (p=0.018). Episodes of hypotension during 48 hours after randomization were similar (4/100 [4%] versus 3/100 [3%]). Thus, UNLOAD demonstrated that in decompensated HF, ultrafiltration safely produces greater weight and fluid loss than intravenous diuretics, reduces 90-day resource utilization for HF, and is an effective alternate therapy.

It is also important to recognize the limitations of the UNLOAD trial. The treatment targets for both diuretics and ultrafiltration were not pre-specified. Although treatment was not blinded, it is unlikely that a placebo effect influenced either weight loss or the improved 90-day outcomes associated with ultrafiltration. The possibility that standard care patients were inadequately treated is diminished by the observation that improvements in symptoms of heart failure, biomarkers, and quality of life were similar in the two treatment groups throughout the study. Furthermore, 43% of patients in the standard care group lost at least 4.5kg during hospitalization, a weight loss greater than that observed in 75% of patients enrolled in the Acute Decompensated Heart Failure National Registry. Although the study did not include measurements of blood volume, plasma refill rate, interstitial salt and water, cardiac performance, or hemodynamics, ultrafiltration was not associated with excessive hypertension or renal or electrolyte abnormalities. The economic impact of ultrafiltration as an initial strategy for decompensated heart failure was also not addressed in this trial. While the costs associated with ultrafiltration during the index hospitalization may exceed those of intravenous diuretics, total cost over time may be lower due to decreased resource utilization for heart failure.

Conclusion
Of the ultrafiltration approaches described, the most practical are veno-venous ultrafiltration techniques in which isonotic plasma is propelled through the filter by an extracorporeal pump. These approaches avoid an arterial puncture, remove a predictable amount of fluid, are not associated with significant hemodynamic instability, and, in the case of peripheral veno-venous ultrafiltration, do not require specialized dialysis personnel. Ultrafiltration has been used in patients with decompensated HF and volume overload refractory to diuretics. These patients generally have pre-existing renal insufficiency and, despite daily oral diuretic doses, develop signs of pulmonary and peripheral congestion. Ultrafiltration and diuretic holiday may restore diuresis and natriuresis. Some patients with volume overload refractory to all available invasive vasoactive therapies have experienced significant improvements of symptoms, hemodynamics, and renal function following ultrafiltration. A strategy of early ultrafiltration and diuretic holiday can result in more effective weight reduction and can shorten hospitalization. Patients should not be considered for ultrafiltration if any of the following apply: venous access cannot be obtained; there is a hypercoagulable state; systolic blood pressure is <80mmHg or there are signs or symptoms of cardiogenic shock; patients require intravenous pressors to maintain an adequate blood pressure; or there is end-stage renal disease, as documented by a requirement for dialysis. Ultrafiltration can be carried out in patients with hemocrit >40% only if it can be proved that hypervolemia is absent.

Many questions regarding the use of ultrafiltration in HF patients remain unanswered and must be addressed in future studies. These include: optimal fluid removal rates in individual patients; the effects of ultrafiltration on cardiac remodeling; the influence of a low oncotic pressure occurring in patients with cardiac cachexia on plasma refill rates; and the economic impact of ultrafiltration to determine whether the expense of disposable filters is offset by the cost savings due to reduced re-hospitalization rates.


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