Early Ultrafiltration in Patients With Decompensated Heart Failure and Diuretic Resistance

Maria Rosa Costanzo, MD, FACC,* Mitchell Saltzberg, MD, FACC,* Jeanne O’Sullivan, RN,* Paul Sobotka, MD, FACC†

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;46:2047–51) © 2005 by the American College of Cardiology Foundation

Traditional diuretic therapy for congestion in acute decompensated heart failure (ADHF) is often ineffective and expensive. The Acute Decompensated Heart Failure National Registry (ADHERE) shows that most ADHF hospitalizations are due to congestion in patients refractory to oral diuretics (1). Despite use of intravenous diuretics in 90% of patients, the average hospitalization for ADHF is 4.3 days, with 42% of the patients discharged with unresolved symptoms, 50% losing ≤5 pounds, and 20% gaining weight during the hospitalization (1). Unresolved congestion may contribute to high readmission rates (1).

Approximately 25% to 30% of patients develop diuretic resistance, defined as reduced diuresis and natriuresis (2). Therapies for diuretic resistance have limited success (3). Renal insufficiency and diuretic resistance are associated with prolonged hospitalization (4,5). Even mild renal insufficiency in patients with left ventricular systolic dysfunction independently predicts morbidity and mortality (6).

Intravenous diuretics can increase pulmonary capillary wedge pressure and systemic vascular resistance and reduce cardiac output and glomerular filtration rate (7,8). Ultrafiltration is an alternative treatment that has been shown to reduce right atrial and pulmonary artery wedge pressures and increase cardiac output, diuresis, and natriuresis without changes in heart rate, systolic blood pressure (SBP), renal function, electrolytes, or intravascular volume (9). Neurohormones drop below control values in the ultrafiltration— but not in the diuretic-treated patients, explaining why ultrafiltration benefits last for three months (9). Recently, the safety and efficacy of peripheral ultrafiltration was demonstrated in fluid-overloaded patients (10).

We sought to determine if early ultrafiltration in ADHF patients with diuretic resistance re-establishes euvolemia and permits hospital discharge in ≤3 days without adverse events and prevents rehospitalization up to three months.

METHODS

Patient population. The subjects were consenting adult ADHF patients hospitalized for ≤12 h and given no vasoactive drugs and ≤1 dose of intravenous diuretic and with the following:

1. Renal insufficiency or diuretic resistance (serum creatinine [sCr] ≥1.5 mg/dl, high daily oral diuretic doses [furosemide >80 mg, torsemide >40 mg, or bumetamide >2 mg], or both) (2,4,11)
2. Fluid overload, defined as ≥2 of the following:
   a. Peripheral or sacral edema (≥2+)
   b.Fluid retention (≥2+ fluid retention)
   c. Anasarca
   d. Pulmonary edema
   e. Hypertension
   f. Anemia
   g. Anuria
   h. Polyuria
   i. Polydipsia
   j. Orthostatic hypotension
   k. Palpitations
   l. Syncope
   m. Dyspnea

From the *Midwest Heart Foundation, Lombard, Illinois; and †CHF Solutions, Brooklyn Park, Minnesota. This study was supported by CHF Solutions, Brooklyn Park, Minnesota. Dr. Costanzo receives grant support from CHF Solutions and a member of the Scientific Advisory Board of CHF Solutions. Dr. Saltzberg receives grant support from CHF Solutions. Dr. Sobotka is Chief Medical Officer for CHF Solutions. Presented in part at the 2004 American Heart Association Scientific Sessions, New Orleans, Louisiana, November 7–10, 2004.

Manuscript received February 18, 2005; revised manuscript received May 4, 2005, accepted May 10, 2005.
in mg/dl)  

(CrCl) was calculated using the Cockroft-Gault equation:

\[
\text{CrCl (men)} = \left(\frac{140 - \text{age}}{72} \times \text{weight in kg}\right) \times \left(\frac{1}{\text{sCr in mg/dl}}\right)
\]

\[
\text{CrCl (women)} = \left(\frac{140 - \text{age}}{72} \times \text{weight in kg}\right) \times \left(\frac{0.85}{\text{sCr in mg/dl}}\right)
\]

Exclusion criteria were:

1. Hematocrit \(\geq 40\%\)
2. End-stage renal disease requiring dialysis
3. Hypercoagulability
4. SBP <85 mm Hg
5. Requirement for intravenous inotropes
6. Participation in another research study or previously in this trial

Study protocol. SCREENING PHASE. After screening and informed consent as approved by the participating hospitals' institutional review boards, patients received physical examinations, electrocardiography, global assessment (12), complete blood count, blood chemistry, B-type natriuretic peptide (BNP) level assessment (Triage BNP Test, Biosite, San Diego, California) (13), partial thromboplastin time, and determination of New York Heart Association functional class, and Minnesota Living With Heart Failure Questionnaire (MLWHFQ) (14). Estimated creatinine clearance (CrCl) was calculated using the Cockroft-Gault equation:

\[
\text{CrCl (men)} = \left(\frac{140 - \text{age}}{72} \times \text{weight in kg}\right) \times \left(\frac{1}{\text{sCr in mg/dl}}\right)
\]

\[
\text{CrCl (women)} = \left(\frac{140 - \text{age}}{72} \times \text{weight in kg}\right) \times \left(\frac{0.85}{\text{sCr in mg/dl}}\right)
\]

PRE-ULTRAFILTRATION PHASE. Heparin was administered by standard protocols. Intravenous diuretics and vasodilators were avoided during ultrafiltration. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, aldosterone antagonists, nitrates, and digoxin were continued.

ULTRAFILTRATION PHASE. Weight and BNP levels were measured at treatment initiation and completion. Blood pressure and heart rate were recorded every 15 minutes for an hour and then every hour. Physical examination and blood chemistries were repeated at 2 and 24 h. After cannulation of the brachial-cephalic vein and standard heparin priming, ultrafiltration was instituted at a maximum rate of 500 cc/h. If SBP fell to \(\leq 80\) mm Hg, ultrafiltration rate was reduced to 200 cc/h. Ultrafiltration was stopped when ADHF symptoms were resolved.

FOLLOW-UP PHASE. Weights, complete blood count, chemistries, and examinations were obtained daily during hospitalization and at 30 and 90 days thereafter. The MLWHFQ and global assessment, medications, and rehospitalizations were recorded at 30 and 90 days. Medications were adjusted by the treating physician.

Statistical analysis. Data are presented as mean values ± SD. The clinical values obtained before initiation of ultrafiltration were compared with those obtained after completion of therapy. Paired comparisons were performed using the Student t test for continuous variables and the McNemar test for ordinal or categorical nonparametric values.

RESULTS

Twenty patients were enrolled over six months. Seventy-five patients were excluded owing to: 1) sCr <1.5 mg/dl and lower-than-required diuretic doses (n = 29); or 2) administration of >1 diuretic dose and/or vasoactive drugs (n = 46).

Fifteen patients were male (75%) and 19 were Caucasian (95%). Age was 74.5 ± 8.2 years (range 50.1 to 85.1 years). Heart failure was ischemic in 15 patients (75%) and non-ischemic in 5 patients. The left ventricular ejection fraction was 31 ± 15% (range 10% to 65%). Edema was present in 80% of patients, ascites in 95%, pulmonary rales in 65%, PND in 75%, jugular venous distention in 95%, and sacral edema in 35%. Ultrafiltration, initiated within 4.7 ± 3.5 h of hospitalization, removed 8,654 ± 4,205 ml of fluid. There were no failed venous cannulations, line malfunctions, phlebitis, or thromboembolism.

Average hospitalization was 3.7 ± 1.8 days. Twelve patients (60%) were discharged in ≤3 days, four (20%) at day four, three (15%) at day five, and one (5%) at day 10. Improvement of volume overload after ultrafiltration persisted at 30 and 90 days (Table 1). Values of the 20 patients before and after ultrafiltration and at 30 and 90 days are shown in Table 2. Weights decreased from 87 ± 23 kg to

<table>
<thead>
<tr>
<th>Clinical Sign/Symptom</th>
<th>Pre-Ultrasound (UF), n (%)</th>
<th>Discharge, n (%)</th>
<th>30 Days, n (%)</th>
<th>90 Days, n (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral edema</td>
<td>16 (80%)</td>
<td>13 (65%)</td>
<td>12 (63%)</td>
<td>7 (35%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Ascites</td>
<td>19 (95%)</td>
<td>15 (75%)</td>
<td>8 (40%)</td>
<td>9 (45%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Pulmonary rales</td>
<td>13 (65%)</td>
<td>6 (30%)</td>
<td>1 (5%)</td>
<td>4 (20%)</td>
<td>0.021</td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnea</td>
<td>15 (75%)</td>
<td>8 (40%)</td>
<td>3 (15%)</td>
<td>4 (20%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Jugular venous distention</td>
<td>19 (95%)</td>
<td>17 (85%)</td>
<td>13 (65%)</td>
<td>6 (30%)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Sacral edema</td>
<td>7 (35%)</td>
<td>8 (40%)</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

UF = ultrafiltration.
81 ± 22 kg and remained lower than pretreatment weights at 30 (84 ± 21 kg) and 90 days (80 ± 18 kg); p = 0.006 (Fig. 1). Pre-ultrafiltration SBP was 120 ± 17 mm Hg (range 99 to 172 mm Hg) and remained unchanged. Pre-ultrafiltration sCr was 2.12 ± 0.60 mg/dl (range 1.0 to 3.6 mg/dl) and remained unchanged. Calculated CrCl was 37.9 ± 13.4 ml/min and remained unchanged (Fig. 2). Blood urea nitrogen was 53 ± 18 mg/dl (range 29 to 100 mg/dl) and remained unchanged. Serum sodium (Na) was 136 ± 4 mg/dl (range 128 to 142 mg/dl) and remained unchanged. In seven patients with serum Na ≤ 135 mg/dl, Na increased from pretreatment values at discharge (p = 0.042) and at 90 days (p = 0.017) (Fig. 3). Serum potassium was 4.2 ± 0.6 mg/dl (range 3.0 to 5.9 mg/dl) and remained unchanged. Median BNP levels decreased after ultrafiltration (from 1,230 to 788 pg/ml) and remained lower at 30 days (815 pg/ml) (p = 0.035).

New York Heart Association functional class IV was present in seven patients (39%) before ultrafiltration, in one

---

### Table 2. Early Ultrafiltration Therapy: Clinical and Laboratory Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-UF</th>
<th>Discharge</th>
<th>30 Days</th>
<th>90 Days</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>87 ± 23</td>
<td>81 ± 22</td>
<td>84 ± 21</td>
<td>80 ± 18</td>
<td>0.006</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>120 ± 17</td>
<td>114 ± 22</td>
<td>120 ± 26</td>
<td>116 ± 24</td>
<td>0.306</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>53 ± 18</td>
<td>54 ± 20</td>
<td>59 ± 23</td>
<td>58 ± 28</td>
<td>0.219</td>
</tr>
<tr>
<td>Cr (mg/dl)</td>
<td>2.12 ± 0.6</td>
<td>2.20 ± 0.8</td>
<td>2.38 ± 1.1</td>
<td>2.18 ± 0.7</td>
<td>0.532</td>
</tr>
<tr>
<td>Na⁺ (mg/dl)</td>
<td>136 ± 4</td>
<td>137 ± 3</td>
<td>137 ± 3</td>
<td>137 ± 2</td>
<td>0.475</td>
</tr>
<tr>
<td>K⁺ (mg/dl)</td>
<td>4.2 ± 0.6</td>
<td>4.1 ± 0.5</td>
<td>4.1 ± 0.6</td>
<td>4.2 ± 0.6</td>
<td>0.646</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>35.3 ± 3.8</td>
<td>35.9 ± 4.1</td>
<td>35.3 ± 4.3</td>
<td>37.0 ± 4.7</td>
<td>0.270</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>11.5 ± 1.3</td>
<td>11.6 ± 1.4</td>
<td>11.5 ± 1.6</td>
<td>12.2 ± 1.4</td>
<td>0.095</td>
</tr>
<tr>
<td>Median BNP (pg/ml)</td>
<td>1,230</td>
<td>788</td>
<td>815</td>
<td>NA</td>
<td>0.03</td>
</tr>
<tr>
<td>NYHA FC IV (%)</td>
<td>39</td>
<td>37</td>
<td>5</td>
<td>11</td>
<td>0.063</td>
</tr>
<tr>
<td>MLWHFQ</td>
<td>70 ± 18</td>
<td>65 ± 21</td>
<td>60 ± 23</td>
<td>51 ± 27</td>
<td>0.003</td>
</tr>
<tr>
<td>Global clinical status</td>
<td>5.7 ± 1.3</td>
<td>1.8 ± 0.8</td>
<td>2.7 ± 1.6</td>
<td>2.5 ± 1.5</td>
<td>0.00003</td>
</tr>
</tbody>
</table>

BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; Cr = creatinine; K = potassium; MLWHFQ = Minnesota Living With Heart Failure Questionnaire; Na = sodium; NYHA FC = New York Heart Association functional class; SBP = systolic blood pressure; UF = ultrafiltration.
(5%) at 30 days, and in two (11%) at 90 days (p = 0.063). Pretreatment MLWHFQ score of 70 ± 18 declined at discharge and 30 and 90 days to 65 ± 21, 60 ± 23.0, and 51 ± 27, respectively (p = 0.003) (Fig. 4). Global assessment improved after ultrafiltration (from 5.7 ± 1.3 to 1.8 ± 0.8) and remained improved at 30 (2.7 ± 1.6) and 90 days (2.5 ± 1.5) (p = 0.00003) (Fig. 5).

In the three months preceding ultrafiltration, ten hospitalizations occurred in nine patients. After ultrafiltration, one patient was readmitted for ADHF within 30 days. Two patients were readmitted between 30 and 90 days for unrelated causes. Medications did not change significantly for the 20 patients (Table 3).

DISCUSSION

Early ultrafiltration in patients with fluid overload and diuretic resistance permitted the discharge of 60% of high-risk ADHF patients in ≤3 days. Aggressive fluid withdrawal (∼8,500 ml) with ultrafiltration was not associated with worsening renal failure, electrolyte abnormalities, or symptomatic hypotension. Early ultrafiltration was associated with a sustained drop in plasma BNP levels. Only one patient was rehospitalized within 30 days. Compared with the shorter hospitalizations reported here, in ADHERE the average hospitalization is 4.3 days and longer than six days in patients with sCr ≥2 mg/dl (1). The economic consequences of a shorter hospitalization were not directly calculated and are not reported in this study.

Renal insufficiency and diuretic resistance in ADHF portend poorer outcomes and higher costs (1,4,11). The study patients had both renal insufficiency and diuretic resistance, as documented by congestion despite chronic diuretics (2,4,5,11). These are the patients most likely to receive intravenous diuretics, which acutely increase neurohormonal activation and decrease glomerular filtration rate (9). In contrast, in the study population, ultrafiltration decreased neurohormonal activation, as indicated by the drop in plasma BNP levels without worsening renal function (9). These findings are consistent with previous observations that plasma norepinephrine, renin, and aldosterone levels drop with ultrafiltration but not with intravenous diuretics (9). The discharge BNP levels of >400 pg/ml may be due to the severe renal dysfunction.

Whereas nine patients required hospitalization for ADHF in the three months preceding ultrafiltration, only one patient required hospitalization for ADHF in the three months after treatment. Similarly, in a previous study, clinical improvements following ultrafiltration persisted for three months (9).

Reversal of the braking phenomenon by diuretic holiday or reduced neurohormonal activation by ultrafiltration may explain improved diuresis and natriuresis (2,9).

Continued improvement for three months after ultrafiltration, without significant medication changes, suggests that ultrafiltration improved natriuresis and diuresis. Normalization of serum Na in the seven hyponatremic patients suggests that ultrafiltration may be valuable for patients with volume overload and hyponatremia.

In summary, the study documents that early ultrafiltration safely and effectively reduces congestion in ADHF with diuretic resistance. A treatment strategy of early ultrafiltration may decrease length of stay and rehospitalizations in high-risk heart failure patients. Clinical benefits of early ultrafiltration last at least three months. Thus, early ultrafiltration may be an alternative to reserving ultrafiltration for patients refractory to all other pharmacologic strategies. In this pilot study the reduction in hospitalization may be due to the combined benefits of ultrafiltration and highly structured continuing care. A prospective randomized study comparing ultrafiltration with standard therapy for ADHF is ongoing to identify effects specifically attributable to ultrafiltration.

Table 3. Number and Percentage of Patients Receiving Drug

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Pre-UF, n (%)</th>
<th>Discharge, n (%)</th>
<th>30 Days, n (%)</th>
<th>90 Days, n (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop diuretic</td>
<td>15 (75)</td>
<td>20 (100)</td>
<td>17 (85)</td>
<td>19 (95)</td>
<td>0.219</td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>4 (20)</td>
<td>6 (30)</td>
<td>5 (25)</td>
<td>5 (25)</td>
<td>1.000</td>
</tr>
<tr>
<td>ACEI</td>
<td>9 (45)</td>
<td>9 (45)</td>
<td>10 (50)</td>
<td>11 (55)</td>
<td>0.687</td>
</tr>
<tr>
<td>ARB</td>
<td>1 (0.5)</td>
<td>2 (10)</td>
<td>2 (10)</td>
<td>3 (15)</td>
<td>0.500</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>10 (50)</td>
<td>11 (55)</td>
<td>9 (45)</td>
<td>12 (60)</td>
<td>0.375</td>
</tr>
<tr>
<td>Nitrates</td>
<td>8 (40)</td>
<td>7 (35)</td>
<td>6 (30)</td>
<td>9 (45)</td>
<td>0.625</td>
</tr>
<tr>
<td>Digoxin</td>
<td>7 (35)</td>
<td>7 (35)</td>
<td>6 (30)</td>
<td>6 (30)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; UF = ultrafiltration.
REFERENCES


