Novel device therapy for HF: ultrafiltration

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Aims of my talk

• Renal dysfunction is mostly related to venous CONGESTION rather than decreased CO in HF patients

• Explain the differences between ultrafiltration and hemofiltration

• The indication of UF: anuria + CHF, increased body weight, preserved BP, resistance to diuretics
Assessing and grading congestion in acute heart failure: a scientific statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine

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Patients with acute heart failure (AHF) require urgent in-hospital treatment for relief of symptoms. The main reason for hospitalization is congestion, rather than low cardiac output. Although congestion is associated with a poor prognosis, many patients are discharged with persistent signs and symptoms of congestion and/or a high left ventricular filling pressure. Available data suggest that a pre-discharge clinical assessment of congestion is often not performed, and even when it is performed, it is not done systematically because no method to assess congestion prior to discharge has been validated. Grading congestion would be helpful for initiating and following response to therapy. We have reviewed a variety of strategies to assess congestion which should be considered in the care of patients admitted with HF. We propose a combination of available measurements of congestion. Key elements in the measurement of congestion include bedside assessment, laboratory analysis, and dynamic manoeuvres. These strategies expand by suggesting a routine assessment of congestion and a pre-discharge scoring system. A point system is used to quantify the degree of congestion. This score offers a new instrument to direct both current and investigational therapies designed to optimize volume status during and after hospitalization. In conclusion, this document reviews the available methods of evaluating congestion, provides suggestions on how to properly perform these measurements, and proposes a method to quantify the amount of congestion present.

« The main reason for hospitalization for acute heart failure is congestion, rather than low cardiac output. »

Congestion impacts renal function!

Gheorghiade et al. Eur J Heart F 2010
Cardio-renal syndromes: report from the consensus conference of the Acute Dialysis Quality Initiative

Claudio Ronco\textsuperscript{1,2*}, Peter McCullough\textsuperscript{3}, Stefan D. Anker\textsuperscript{4,5}, Inder Anand\textsuperscript{6}, Nadia Aspromonte\textsuperscript{7}, Sean M. Bagshaw\textsuperscript{8}, Rinaldo Bellomo\textsuperscript{9}, Tomas Berl\textsuperscript{10}, Ilona Bobek\textsuperscript{1}, Dinna N. Cruz\textsuperscript{1,2}, Luciano Daliento\textsuperscript{11}, Andrew Davenport\textsuperscript{12}, Mikko Haapio\textsuperscript{13}, Hans Hillege\textsuperscript{14}, Andrew A. House\textsuperscript{15}, Nevin Katz\textsuperscript{16}, Alan Maisel\textsuperscript{17}, Sunil Mankad\textsuperscript{18}, Pierluigi Zanco\textsuperscript{19}, Alexandre Mebazaa\textsuperscript{20}, Alberto Palazzuoli\textsuperscript{21}, Federico Ronco\textsuperscript{11}, Andrew Shaw\textsuperscript{22}, Geoff Sheinfeld\textsuperscript{23}, Sachin Soni\textsuperscript{1,24}, Giorgio Vescovo\textsuperscript{25}, Nereo Zamperetti\textsuperscript{26}, and Piotr Ponikowski\textsuperscript{27} for the Acute Dialysis Quality Initiative (ADQI) consensus group
Cardio-renal type I

« acute »

Acute heart disease or procedures
- Acute decompensation
- Ischemic insult
- Coronary angiography
- Cardiac surgery

Acute renal injury
- Acute hypoperfusion
- Reduced oxygen delivery
- Necrosis/apoptosis
- Decreased GFR
- Resistance to ANP/BNP

Biomarkers
- KIM-1
- Cystatin-C
- N-GAL
- Creatinine

Hemodynamically mediated damage

Decreased perfusion
- Increased venous pressure

Exogenous factors
- Contrast media
- ACE inhibitors
- Diuretics

Toxicity
- Vasoconstriction

Humorally mediated damage

RAA activation,
- Na + H₂O retention,
- vasoconstriction

Humoral factors

Sympathetic activation

Hormonal factors

Natriuresis

Immune mediated damage

Caspase activation
- Apoptosis

Monocyte activation

Endothelial

Renal function is impaired as a function of Central Venous Pressure (CVP) in Chronic HF.
Effects of CVP, CI, SBP and PCWP on worsening renal function in Acute Heart Failure patients

Mullens et al. JACC 2009, 53:589-596
ROC curves of CVP and CI in WRF development

Mullens et al. JACC 2009, 53:589-596
High CVP impacts renal function

Effect of initial CVP on rehospitalization and long-term death

Kaplan-Meier analysis for cardiac rehospitalization (A) and all-cause mortality (B) according to central venous pressure at presentation.

H Uthoff et al, EJHF 2010
Ultrafiltration vs hemofiltration vs hemodialysis
Aims of renal replacement therapies

• Clear the blood from many small molecules (urea, creatinine, K+)
  • DIALYSIS (gradient of concentration)

• Remove fluids (salt & water)
  • FILTRATION (gradient of pressure)
Indications

• **Dialysis**
  – Only if there is a true glomerular dysfunction, urea > 50 mmol/L or creat clear < 10 ml/min or creat > 500 µmol/L

• **Ultrafiltration**
  – Only if there is evidence of fluid retention that is unresponsive to diuretics
Transient versus continuous

- Dialysis is TRANIENT (often no need to remove fluid), may alter hemodynamics

- Hemodialysis & ultrafiltration are CONTINUOUS (clear small molecules +/- fluid if needed), hardly alter hemodynamics
Hemofiltration (CVVH)

Ultrafiltration (salt and water)

Continuous veno-venous ultrafiltration

Ultrafiltration replacement fluid

Ultrafiltration (salt, water, urea, creat)

Ultrafiltration (salt and water)
- Based on the principle of convective solute transport
- Water and substances (up to 20000) pass across highly permeable membrane (~ glomerular filtration) + adsorption
- Primary purpose in HF – remove of fluid excess (not dialysis !)
<table>
<thead>
<tr>
<th>Potential Complications of Extracorporeal Pumped Ultrafiltration Machines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air embolus</td>
</tr>
<tr>
<td>Hemorrhage from venous return disconnection</td>
</tr>
<tr>
<td>Hemorrhage from hollow fiber blood leak</td>
</tr>
<tr>
<td>Hemorrhage complicating systemic anticoagulation</td>
</tr>
<tr>
<td>Membrane bioincompatibility</td>
</tr>
<tr>
<td>Hemolysis and hyperkalemia</td>
</tr>
<tr>
<td>Catheter-related complications (ie, infections, stenoses, thromboses)</td>
</tr>
<tr>
<td>Excess ultrafiltration resulting in hypotension, prerenal azotemia, or acute renal failure</td>
</tr>
<tr>
<td>Allergic reactions to the extracorporeal circuit</td>
</tr>
</tbody>
</table>
Hemofiltration (CVVH)

Ultrafiltration (salt, water, urea, creat)

Dialysis fluid

Ultrafiltration replacement fluid

Continuous veno-venous

Ultrafiltration and dialysate
Hemodialysis

Forni LG, NEJM 1997, 336 : 1333

+ glucose/bicarbonate
**Table 1. Typical Composition of Hemofiltration Replacement Fluid.**

<table>
<thead>
<tr>
<th>Component</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>140 mmol/liter</td>
</tr>
<tr>
<td>Potassium</td>
<td>0</td>
</tr>
<tr>
<td>Calcium</td>
<td>1.6</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.75</td>
</tr>
<tr>
<td>Chloride</td>
<td>101</td>
</tr>
<tr>
<td>Lactate</td>
<td>45</td>
</tr>
<tr>
<td>Glucose</td>
<td>11</td>
</tr>
</tbody>
</table>

*The values shown are for Gambro Hemofiltrasol 22. Potassium chloride is added to the solution immediately before use in concentrations of up to 4 mmol per liter, depending on the serum potassium concentration. To convert the value for calcium to milligrams per deciliter, divide by 0.25; to convert the value for magnesium to milliequivalents per liter, divide by 0.5; and to convert the value for glucose to milligrams per deciliter, divide by 0.05551.*
Advantages and disadvantages of renal replacement therapies

<table>
<thead>
<tr>
<th>Type</th>
<th>Complexity</th>
<th>Efficiency</th>
<th>Cost</th>
<th>Anticoagulant Therapy</th>
<th>Risk of Hemorrhage</th>
<th>Risk of Infection</th>
<th>Extracellular-Fluid Volume Control</th>
<th>Use in Hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritoneal dialysis</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
<td>No</td>
<td>Low</td>
<td>High</td>
<td>Moderate</td>
<td>Yes</td>
</tr>
<tr>
<td>Intermittent hemodialysis</td>
<td>Moderate</td>
<td>High</td>
<td>Low</td>
<td>Yes</td>
<td>Moderate</td>
<td>Low</td>
<td>Intermittent</td>
<td>No</td>
</tr>
<tr>
<td>Continuous arteriovenous hemofiltration</td>
<td>Moderate</td>
<td>Low and variable</td>
<td>Moderate</td>
<td>Yes</td>
<td>Moderate</td>
<td>Low</td>
<td>Good</td>
<td>No</td>
</tr>
<tr>
<td>Continuous arteriovenous hemodialysis with filtration</td>
<td>High</td>
<td>Moderate and variable</td>
<td>High</td>
<td>Yes</td>
<td>Moderate</td>
<td>Low</td>
<td>Good</td>
<td>Variable</td>
</tr>
<tr>
<td>Continuous venovenous hemofiltration</td>
<td>Moderate</td>
<td>High</td>
<td>Moderate</td>
<td>Yes</td>
<td>Moderate</td>
<td>Low</td>
<td>Good</td>
<td>Yes</td>
</tr>
<tr>
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<td>High</td>
<td>High</td>
<td>High</td>
<td>Yes</td>
<td>Moderate</td>
<td>Low</td>
<td>Good</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Forni LG, NEJM 1997, 336 : 1333
Ultrafiltration to treat fluid retention and organ’s congestion

Clinical data
Peripherally-Inserted Ultrafiltration (CHF Solutions System S-100)
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

JACC 2005; 46:2047-51

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. Enlarged liver or ascites
   c. Pulmonary rales, paroxysmal nocturnal dyspnea (PND), or orthopnea
   d. Jugular venous distention ≥7 cm

Exclusion criteria were:

1. Hematocrit ≥40%
2. End-stage renal disease requiring dialysis
3. Hypercoagulability
4. SBP <85 mm Hg
5. Requirement for intravenous inotropes

Table 1. Clinical Signs and Symptoms of Volume Overload

<table>
<thead>
<tr>
<th>Clinical Sign/Symptom</th>
<th>Pre-Ul, 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.
# 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

JACC 2005; 46:2047-51

## 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.**
Ultrafiltration

A New Approach Toward Mechanical Diuresis in Heart Failure

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José A. Tallaj, MD

Birmingham, Alabama

JACC Vol. 46, No. 11, 2005
December 6, 2005:2052–3
Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure

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Mitchell T. Saltzberg, MD, FACC,* Mariell L. Jessup, MD, FACC,‡ Bradley A. Bart, MD, FACC,§
John R. Teerlink, MD, FACC,‖ Brian E. Jaski, MD, FACC,¶ James C. Fang, MD, FACC,#
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Michael P. Schollmeyer, DVM,§§ Paul A. Sobotka, MD, FACC,§§ for the UNLOAD Trial Investigators

Lombard and Chicago, Illinois; Detroit, Michigan; Philadelphia, Pennsylvania; Minneapolis and Brooklyn Park, Minnesota; San Francisco and San Diego, California; Boston, Massachusetts; Baltimore, Maryland; and Columbus, Ohio
Methods

Inclusion Criteria

- ≥ 18 years of age
- Hospitalized with evidence of volume overload by at least two of the following:
  - peripheral edema ≥ 2+
  - jugular venous distension ≥ 7 cm
  - radiographic pulmonary edema or pleural effusion
  - enlarged liver or ascites
  - pulmonary rales, paroxysmal nocturnal dyspnea or orthopnea
- Randomization within 24 hours of hospitalization
Methods

Study Procedures

- **Ultrafiltration arm:**
  - Ultrafiltration rate up to 500 cc/hour
  - Duration/rate of fluid removal decided by treating physicians
  - IV diuretics prohibited during ultrafiltration

- **Standard Care arm:**
  - IV diuretics as bolus or continuous infusions
  - IV doses at least 2 times daily PO dose for the first 48 hours after randomization
UNLOAD

200 pts with ADHF with ≥ 2 signs of fluid overload;
UF (n=100) vs SOC (n=100) NYHA class: 3.4;
LVEF ≤ 40% in 70% pts; no of hosp < 12 months – 1.6

**Primary end-points**

- Weight Loss (kg)
  - UF: m=5.0, Cl=±0.68, n=83
  - SC: m=3.1, Cl=±0.75, n=84
  - p=0.001

- Dyspnea Score
  - UF: m=6.4, Cl=±0.11, n=80
  - SC: m=6.1, Cl=±0.15, n=83
  - p=0.35

- Serum Creatinine Changes (mg/dL)
  - UF: 8h, 24h, 48h, 72h, 10d, 30d, 90d
  - SC: 8h, 24h, 48h, 72h, 10d, 30d, 90d

**Values:**
- UF: 72, 90, 69, 47, 86, 71, 75, 66
- SC: 84, 91, 75, 52, 90, 75, 67, 62
Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure

p = 0.037

<table>
<thead>
<tr>
<th>Days</th>
<th>Ultrafiltration Arm</th>
<th>Standard Care Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>88</td>
<td>86</td>
</tr>
<tr>
<td>20</td>
<td>85</td>
<td>83</td>
</tr>
<tr>
<td>30</td>
<td>80</td>
<td>77</td>
</tr>
<tr>
<td>40</td>
<td>77</td>
<td>74</td>
</tr>
<tr>
<td>50</td>
<td>75</td>
<td>74</td>
</tr>
<tr>
<td>60</td>
<td>72</td>
<td>69</td>
</tr>
<tr>
<td>70</td>
<td>70</td>
<td>66</td>
</tr>
<tr>
<td>80</td>
<td>66</td>
<td>63</td>
</tr>
<tr>
<td>90</td>
<td>64</td>
<td>59</td>
</tr>
</tbody>
</table>

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
Conclusions

• UNLOAD is the first trial to demonstrate the superiority of UF compared to iv diuretics for the treatment of volume overload in hospital.

• These results challenge current practice and guidelines.
In summary

- In acute heart failure, renal function is often impaired:
  - If 1) UO is markedly reduced with 2) moderate increase in urea or creatinine and in liver enzymes and 3) unresponsiveness to diuretics: avoid high dose diuretics: start hemofiltration
  
  - If 1) UO is markedly reduced with 2) marked increase in urea or creatinine (alteration in glomerular filtration): dialysis will likely be needed
Aims of my talk

• Renal dysfunction is mostly related to venous CONGESTION rather than decreased CO in HF patients

• Explain the differences between ultrafiltration and hemofiltration

• The indication of UF: anuria + CHF, increased body weight, preserved BP, resistance to diuretics