Management of Volume Overload in the Hospitalized Patient with Heart Failure: (Drugs) and Devices

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Disclosures

• Employee: Advocate Heart Institute
• Consultant: Respocardia, Abbott, Axon Technologies, Paragate, CHF-Solutions, Fresenius
Lets Make it Simple!!!!
What in the World is the Cardiorenal Syndrome???

The kidney behaves as if there were dehydration when no dehydration is present.

We see this as:
Reduced glomerular filtration rate and increased sodium avidity (diuretic resistance)

http://www.nhlbi.nih.gov/meetings/workshops/cardiorenal-hf-hd.htm

Courtesy of Jeffrey Testani, M.D., M.T.R.
Why Ultrafiltration?
Because ADHF Patients Have Loop Diuretic Resistance!!!

Box 1 | Definitions of diuretic resistance
- Persistent congestion despite adequate and escalating doses of diuretic with >80 mg furosemide per day\(^{107}\)
- Amount of sodium excreted as a percentage of filtered load <0.2\(^{108}\)
- Failure to excrete at least 90 mmol of sodium within 72 h of a 160 mg oral furosemide dose given twice daily\(^{109}\)

Box 2 | Metrics of diuretic response
- Weight loss per unit of 40 mg furosemide (or equivalent)\(^{5,51}\)
- Net fluid loss per milligram of loop diuretic (40 mg of furosemide or equivalent) during hospitalization\(^6\)
- Natriuretic response to furosemide as the ratio of urinary sodium to urinary furosemide\(^{52}\)

Range of Approaches to Volume Management

- **Device-Based Volume Removal Methods**
  - Decreased Kidney Interstitial Pressure
  - Increased Blood Flow into Kidney
  - Decreased Kidney Interstitial Pressure

- **Pharmacological Therapy**
  - Treat Symptoms of Volume Overload
  - Improve Native Kidney Function

- **Independent of kidney function**
  - Ultrafiltration
  - Paragate
  - Sequana

- **Increase Blood Flow out of Kidney**
  - IASD

- **Procyron Impella/Nupulse Cardionomics/Neurotronik**

- **Magenta**

- **Diuretics**

- **RenalGuard**

- **Increased Blood Flow into Kidney**

- **Decreased Kidney Interstitial Pressure**

- **Signs/Symptoms of HF Hospitalizations Morbidity and Mortality**

- **Treat Symptoms of Volume Overload**
Ultrafiltration can remove fluid from the blood at the same rate that fluid can be naturally recruited from the tissue.

The transient removal of blood elicits a compensatory mechanism, called plasma or intravascular refill (PR), aimed at minimizing this reduction\(^1,2\)

Reciprocal Pathways Linking Heart Failure, Renal Dysfunction, and Congestion in the CRS

Courtesy of Amir Kazory, Division of Nephrology, Hypertension, and Renal Transplantation, University of Florida, Gainesville, Florida, USA
## Comparative Characteristics of Loop Diuretics and Isolated Ultrafiltration

<table>
<thead>
<tr>
<th>Loop Diuretics</th>
<th>Isolated Ultrafiltration</th>
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<tbody>
<tr>
<td>Direct neurohormonal activation</td>
<td>No direct neurohormonal activation</td>
</tr>
<tr>
<td>Elimination of hypotonic urine</td>
<td>Removal of isotonic plasma water</td>
</tr>
<tr>
<td>Unpredictable elimination of sodium and water</td>
<td>Precise control of rate and amount of fluid removal</td>
</tr>
<tr>
<td>Development of diuretic resistance with prolonged administration</td>
<td>Restoration of diuretic responsiveness</td>
</tr>
<tr>
<td>Risk of hypokalemia and hypomagnesemia</td>
<td>No effect on plasma concentration of potassium and magnesium</td>
</tr>
<tr>
<td>Peripheral venous access</td>
<td>Peripheral or central venous catheter</td>
</tr>
<tr>
<td>No need for anticoagulation</td>
<td>Need for anticoagulation</td>
</tr>
<tr>
<td>No extracorporeal circuit</td>
<td>Need for extracorporeal circuit</td>
</tr>
</tbody>
</table>

Two Contemporary Ultrafiltration Devices

Aquadex System 100

CHIARA Device

# UF Clinical Trials: Overview of Study Designs and Key Findings

<table>
<thead>
<tr>
<th>Study Name, Publication Year</th>
<th>Study Group</th>
<th>UF Arm</th>
<th>Comparison Arm</th>
<th>Primary Efficacy Endpoint</th>
<th>Primary Endpoint Result</th>
<th>Reported Clinical Outcomes*</th>
<th>Mortality</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAPID-HF, 2005 (40)</td>
<td>N = 40</td>
<td>Single, 8-or course, median duration 8 h, median volume removed 3,213 ml</td>
<td>Standard IFT therapies determined by treating physician</td>
<td>Weight loss 24 h post-consent</td>
<td>Weight loss approximately 0.25 kg (UF) vs. – 7 kg (standard care), p = 0.24</td>
<td>Index length of stay: days (UF) vs. 5 days (standard care), p = 0.5</td>
<td>No significant difference in death, bleeding (1 UF vs. 7 standard care), p = 0.032</td>
<td>UF group: catheter infection, UF related, 5 catheter clots, 1 patient transitioned to hemodialysis due to insufficient response to UF</td>
</tr>
<tr>
<td>UNLOAD, 2007 (33)</td>
<td>N = 200</td>
<td>Hospitalized with HF, &lt;2 signs of fluid overload</td>
<td>Aquadex System 100/ Mean fluid removal rate 241 ml/h for 12.3 ± 12 h</td>
<td>Standard care: IV diuretic agents. For each 24-h period, at least twice the pre-hospitalization daily oral dose</td>
<td>Weight loss and dyspnea assessment at 48 h after randomization</td>
<td>No significant difference in death, bleeding (1 UF vs. 7 standard care), p = 0.032</td>
<td>UF group: catheter infection, 5 catheter clots, 1 patient transitioned to hemodialysis due to insufficient response to UF</td>
<td></td>
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<tr>
<td>ADDRESS-HF, 2012 (53)</td>
<td>N = 188</td>
<td>Hospitalized with HF, &lt;2 signs of congestion, and recent ≥0.3 mg/dl ICD increase</td>
<td>Aquadex System 100/ at a fixed rate of 200 ml/h</td>
<td>SPT with intravenous diuretic agents dosed to maintain urine output 3-5 ml/day</td>
<td>Bivariate response of change in iCtCr and change in weight 96 h after randomization</td>
<td>No significant difference in death, bleeding (1 UF vs. 7 standard care), p = 0.032</td>
<td>UF group: catheter infection, 5 catheter clots, 1 patient transitioned to hemodialysis due to insufficient response to UF</td>
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<td>COUPE, 2014 (53)</td>
<td>N = 56</td>
<td>NYHA III or IV, LVEF ≤40%, ≥4 kg weight gain from peripheral fluid overload, over 2 months</td>
<td>Dedica device</td>
<td>Mean treatment duration 19 ± 90 h</td>
<td>Intravenous diuretic agents according to guideline recommendations (standard care)</td>
<td>HF rehospitalization at 1 yr</td>
<td>No significant difference in death, bleeding (1 UF vs. 7 standard care), p = 0.032</td>
<td>UF group: catheter infection, 5 catheter clots, 1 patient transitioned to hemodialysis due to insufficient response to UF</td>
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<tr>
<td>AVOID-HF, 2016 (56)</td>
<td>N = 224</td>
<td>Hospitalized with HF, &gt;2 criteria for fluid overload, receiving daily oral loop diuretic agents</td>
<td>ALF with Aquadex FilloFlow System; adjustments per protocol guidelines on the basis of vital signs and renal function</td>
<td>Mean fluid removal rate 138 ± 47 ml/h for 80 ± 53 h</td>
<td>Time to first HF event (HF rehospitalization or unscheduled outpatient emergency treatment with intravenous loop diuretic agents or UF) within 90 days of hospital discharge</td>
<td>No significant difference in death, bleeding (1 UF vs. 7 standard care), p = 0.032</td>
<td>UF group: catheter infection, 5 catheter clots, 1 patient transitioned to hemodialysis due to insufficient response to UF</td>
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<td>ULTRADISCO, 2011 (45)</td>
<td>N = 30</td>
<td>Hospitalized for HF; &gt;2 peripheral edema, ≥1 other criteria for volume overload</td>
<td>PRISMAI Mean treatment duration 46 h, cumulative fluid loss 9.7 ± 2.9 l</td>
<td>Intravenous diuretic agents</td>
<td>Time to first HF event (HF rehospitalization or unscheduled outpatient emergency treatment with intravenous loop diuretic agents or UF) within 90 days of hospital discharge</td>
<td>No significant difference in death, bleeding (1 UF vs. 7 standard care), p = 0.032</td>
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CARRESS
Changes in Serum Creatinine and Weight at 96 Hours (Bivariate Response)

Direct comparison of ultrafiltration to pharmacological decongestion in heart failure: a per-protocol analysis of CARRESS-HF

Justin L. Grodin1,*, Spencer Carter2, Bradley A. Bart3, Steven R. Goldsmith3, Mark H. Drazner1, and W.H. Wilson Tang4

EDITORIAL:
Better Late than Never: The True Results of CARRESS-HF
Maria Rosa Costanzo, M.D., F.E.S.C.1, Amir Kazory, M.D.2
A per-protocol analysis of the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial ($n=188$) was performed. Participants were included if randomized to UF and had UF output collected, or if randomized to the pharmacological arm and had urine but not UF output collected. Using these definitions, there were 163 participants at 24 h, 156 at 48 h, 129 at 72 h, and 106 at 96 h. UF was associated with higher cumulative fluid loss ($P=0.003$), net fluid loss ($P=0.001$), and relative reduction in weight ($P=0.02$). UF was also associated with higher serum creatinine and blood urea nitrogen by 72 h ($P$-interaction $<0.05$ for both), lower serum sodium by 48 h ($P$-interaction $<0.01$) and increased plasma renin activity by 96 h ($P=0.04$). The pharmacological arm was associated with higher serum bicarbonate after 24 h ($P$-interaction $<0.002$). There were no differences in 60-day outcomes between the UF and pharmacological arms.
This Says it All!!!

- 14/94 (15%) in the SPT and 22/94 (23%) in the UF group achieved OVS
- Of the 288 patients 76/94 (80%) SPT and only 30/94 (32%) of UF patients remained in the study up to the 96 hours evaluation of the primary end-point
- In the UF group filter clotting occurred before 24 hours in 13 patients, before 48 hours in 5, before 72 hours in 3 and before 96 hours in 2:
  - 23 filter clotting events resulting in termination of therapy!!!
- In 28/94 (28%) patients UF was terminated due to “MD Decision”(???) independent of:
  - Achievement of OVS
  - Hypotension
  - Hemodynamic Instability
  - Volume Depletion
  - Increased creatinine
  - Filter Clotting
  - Vascular Access Failure

UF Rates in CARRESS-HF per 24 Hour Period

The mandated UF rate was 200 ml/h!

• Refill rate drops as volume status becomes more “normal”
• As refill rate drops, risk of intra-vascular volume depletion rises

Marenzi et al., J Am Coll Cardiol 2001;38:963–8
This is what I see with UF!!

Patient GF; UF rate 150 ml/h
Decision Analytic Framework Adapted from Bradley et al.

1. Costanzo MR, Fonarow GC, Rizzo JA et al. Submitted
Model Results for Rehospitalization Costs to Treating Hypervolemia in HF Patients with either UF or IV Diuretics

Costanzo MR, Fonarow GC, Rizzo JA et al. Submitted
New Gentle UF concept: gentle ultrafiltration complementary to low-dose i.v. diuretics with peripheral single needle access

Patient cohort in Pure-HF: Symptomatic HF patients admitted to the hospital due to congestion, not fully responsive to diuretic therapy.
→ 864 patients in 30 centers in 7 countries

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<th>Ultrafiltration group</th>
<th>Control group</th>
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<td>Peripheral UF + low-dose i.v. diuretics</td>
<td>Guideline-directed medical therapy incl. i.v. diuretics</td>
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<tr>
<td>1-7 UF sessions (6-10 h/day-time session, 1-10 days)</td>
<td>Treatment algorithm based on the current dose at index hospitalization, urine output and clinical assessment</td>
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Follow-up: 30- and 90-days
Primary endpoint:
→ Heart failure event in 90 days after discharge
→ Cardiovascular death in 90 days after randomization

HF event: a HF rehospitalization OR unscheduled outpatient visit OR emergency room treatment with i.v. diuretics or UF
Placed in the descending thoracic aorta, Aortix was designed specifically for the needs of the ADHF patient:

**SIGNIFICANTLY REDUCED RISKS:**
- < 10 minute percutaneous procedure
- Downstream of the carotids / does not sit across valve
- Securely anchored
- Fails safely

**HIGH QUALITY OF LIFE:**
- Quick recovery and ambulation
- Small form-factor
- Extended battery life

**IMPROVED HEMODYNAMICS**:
- **21%** Ejection Fraction
- **22%** Stroke Volume
- **-9%** Filling Pressure
- **10X** Renal Function

*Aortix FIH experience. * = p < 0.05 paired t-test
• High Risk PCI Patients
• Significant Cardiac Disfunction
• Moderate-severe renal dysfunction

Aortix First In Human Trial:

Principal Investigator:
- Manesh Patel, M.D. Duke University

Clinical Site:
Asuncion, Paraguay-Sanatorio Italiano
Adrian Ebner, M.D.
Transcatheter Renal Venous Decongestion System: Catheter and Console

TRVD™ Pump Head & Catheter Handle

Magenta Control Console

Pressure Sensor
Transcatheter Renal Venous Decongestion (TRVD™) for Congestive Heart Failure

Severely congested kidney in heart failure

- High Venous Pressure
  - Poor renal perfusion
  - Poor renal function
  - Fluid retention

Decompressed kidney with flow pump

- Normal Venous Pressure
  - Improved renal perfusion
  - Improved renal function
  - Fluid removal
Direct Peritoneal Sodium Removal

• When we think of mechanical fluid/sodium removal we normally think of veno-venous ultrafiltration
  • Ultrafiltration of water/small molecules through an extracorporeal artificial membrane that blood is passed over

• Peritoneal membrane can also be used for this
  • This is the basis of peritoneal dialysis

• Peritoneal dialysis is designed to use large volumes of dialysis solution passed over the peritoneal membrane to clean the blood
  • Not optimized for sodium/water removal and impractical for routine use in HF

• Direct Peritoneal Sodium Removal optimizes the peritoneal solution for high salt and water removal with low volumes
  • Combined with a fully implantable pump and access port for chronic use
Direct Peritoneal Sodium Removal with the alfa pump System

alfa pump is a fully implanted, automatic, programmable pump that is transcutaneously charged and can be adjusted wirelessly.
alfapump Has Been Clinically Validated

System is CE-marked for refractory ascites and malignant ascites, with over 600 systems implanted in patients

Direct Sodium Removal – PD Fluid Volume Removed

Administration of 1L of dialysate with two hour dwell results in ~2L of ultrafiltrate removal

Protocol Refinement Pigs

Protocol Pigs (two hour dwell)

PD fluid volume

Fluid Volume (L)

Time (min)

0 50 100 150 200 250 300

1.0 1.2 1.4 1.6 1.8 2.0 2.2 2.4 2.6

PD fluid (ml)

Pig number

1 2 3 4 5 6 7 8 9 10

0 500 1000 1500 2000 2500

Courtesy Dr. Jeffrey Testani, M.D., M.T.R.
Direct Sodium Removal – Evolution of Na Removal

Na Removal Over 6 Hours (protocol refinement pigs)

Na Concentration in PD Fluid (protocol refinement pigs)

Total Na Quantity

Na mmol/L

Time (min)

0 100 200 300 400

0 50 100 150 200 250

Courtesy Dr. Jeffrey Testani, M.D., M.T.R.
Direct Sodium Removal – Effective Na Removal: Protocol Pigs

Sodium removed after 2 hour dwell is equivalent to 2 days sodium consumption

Total amount of Na removed with 2 hour PD dwell

N\(a\) (mg)

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<td>4</td>
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<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>2000</td>
<td>4000</td>
<td>6000</td>
<td>8000</td>
<td>10000</td>
<td>12000</td>
<td>14000</td>
<td>16000</td>
</tr>
</tbody>
</table>

N\(a\) (mg)

| Total amount of Na removed with 2 hour PD dwell |

Courtesy Dr. Jeffrey Testani, M.D., M.T.R.
DPSR: Substantial Reduction in Blood Volume Possible

*intraperitoneal volume was determined serially using indicator dilution technique with I-131 radiolabeled albumin (Daxor Corp., NY).

**plasma volume measured with I-131 radiolabeled albumin (Daxor Corp., NY) prior to and after cycling completion.
Mechanism of Action

Osmotic
Peritoneal Dialysis

Hydrostatic
Implantable Peritoneal Ultrafiltration

Flesner - Blood Purif 1992 10 136–14
Implantable Peritoneal Ultrafiltration

Absorption of Excess Systemic Isotonic Fluids by Applying Hydrostatic Pressure Gradient

- Continuous
- Non aggressive
- Configurable
- Monitoring features
- No circulation contact
- Low infection risk
Laparoscopic Procedure

Short Procedure, No Anchoring, Single Access, Bladder Approach
Conclusions

➢ It is an exciting time for fluid management of congested heart failure patients

➢ The focus is shifting from the unpredictable removal of hypotonic fluid by diuretics to decongestive methods that avoid intravascular volume depletion and consequent renal hypoperfusion

➢ The novel fluid management methods have variable degrees of invasiveness ranging from the requirement of a peripheral venous access and a urinary catheter, to that for intravascular and intraperitoneal implant procedures

➢ Overall novel fluid management therapies are at an early stage of development, with some still in pre-clinical trials and others having been studied in first-in-man trials with a small number of subjects.

➢ Further investigation of novel fluid management methods should focus on assessment of:
  ❖ Safety
  ❖ Ease of use
  ❖ Candidates selection
  ❖ Reproducibility of effects across heart failure patient populations
  ❖ Costs