Ultrafiltration for Refractory Volume overload

ACOI Hospitalist 2016

John Prior
Disclosures

Nothing to declare
Case

65 yo woman admitted for ADHF – DOE and peripheral edema, PND and orthopnea

PE – edema, +JVD, rales, enlarged apex with Systolic Murmurm of MR

Echo – moderate pulm HTN, moderate MR and EF 55%
Case

BP 122/ HR 88  RR 22
Admission labs – Creatinine 2.4 (1.5), Na 129, and Hg 9.5
Outpatient meds – lisinopril 20, metoprolol 50 and furosemide 40 2X day
What is her diagnosis?
How to manage volume?
ADHF - Background

#1 admission diagnosis in patients > 65 yo
Inpatient mortality – 4%
30 day readmission rate - 27%
Renal Disease in patients with ADHF

ADHERE – 105,000 - 30% with GFR < 45 ml/min

The worse the heart failure the worse the average GFR

Lower GFRs are associated with worse outcomes (inpatient and outpatient)
Cardiorenal Syndromes

Definition – Negative effects of heart or kidney dysfunction on the other organ

CRS 1 – rapid worsening of cardiac function leading to AKI
CRS 2 – chronic cardiac dysfunction leads to CKD
CRS 3 – AKI leads to cardiac dysfunction
CRS 4 – CKD and cardiovascular disease
CRS 5 – Systemic illness affecting heart and kidney
AKI in ADHF

AKI (creatinine elevation >0.2) in all patients has been shown (not always) to predict poor outcomes.

Admission and discharge GFR are best outcome predictors in ADHF.

Rarely due to over diuresis in 1st 72 hrs, elevated CVP and IAP are predictive of AKI and often present in the patient with AKI.
Pathophysiology of CRS

Low flow state - poor CO leads to renal hypoperfusion and worsening GFR
therapies directed at improving flow have not lead to improved outcomes
ESCAPE – use of PA catheters to diagnose and aid in therapy of ADHF. No correlation between CO and GFR. RAP was the strongest predictor of outcomes and GFR (venous congestion)
Intra-abdominal hypertension
Dual hemodynamic pathways for acute cardiorenal syndrome.

**Arterial underfilling**
- Decreased cardiac output
- Decreased effective circulating volume
- Decreased RBF, RPF
- Activation of RAAS, SNS
- Inflammatory pathways

**Heart**
- Venous congestion and venous hypertension, raised IAP
- Decreased AV perfusion gradient
- Kidney interstitial edema
- Activation of RAAS, SNS
- Inflammatory pathways

**Kidney**
- Decreased GFR
- Na and H₂O retention
- Increased edema, preload
- Increased afterload
Impact of Venous Congestion on Glomerular Net Filtration Pressure

**Forces**

1. **Favoring Filtration**
   - Glomerular-capillary hydrostatic pressure, $P_{GC}$
     - Normal: 60 mmHg, 58 mmHg
     - RA pressure: 55 mmHg, 63 mmHg

2. **Opposing Filtration**
   - a. Hydrostatic pressure in Bowman’s capsule, $P_{BC}$
     - Normal: 15 mmHg, 15 mmHg
     - RA pressure: 15 mmHg, 15 mmHg
   - b. Oncotic pressure in glomerular capillaries, $\pi_{GC}$
     - Normal: 21 mmHg, 33 mmHg
     - RA pressure: 21 mmHg, 33 mmHg

**Net filtration pressure (1-2)**

- **Filtration pressure:**
  - Normal: 24 mmHg, 10 mmHg
  - RA pressure: 19 mmHg, 15 mmHg
Baseline Serum Creatinine Level and IAP

Intra-abdominal Pressure  
≥ 8 mmHg  
< 8 mmHg

p = 0.009
Transvesical Method for Measuring Intra-Abdominal Pressure

Mullens, W. et al. J Am Coll Cardiol 2008;51:300-306
Intra Abdominal Hypertension

Mullens intervention trial – refractory ADHF patients (9) with elevated IAP received paracentesis or ultrafiltration which resulted in a decrease in IAP 13 to 7. Creatinine improved from 3.4 to 2.4 and there was no change in hemodynamics.
ADHF – Goals of Therapy

1. Adequate decongestion
2. Improved patient outcomes
3. Decreased hospital readmissions
4. No significant complications
Decongestion

Patients admitted for ADHF are often inadequately decongested

European registry data

If therapies are compared, they should have similar degrees of decongestion
Change in body weight at discharge based on Acute Decompensated Heart Failure National Registry database.

Kazory A CJASN 2013;8:1816-1828
DOSE Trial

308 patients with ADHF  RCT comparing low dose (outpt dose) vs. high dose (2.5X outpt dose) q12 bolus furosemide

Bolus was compared to continuous infusion

High dose better for relief of symptoms and decongestion

Bolus and continuous equal

STANDARD DIURETIC DOSE 2.5X OUTPATIENT
## Table 2. Secondary End Points for Each Treatment Comparison.*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Bolus Every 12 Hr (N=156)</th>
<th>Continuous Infusion (N=152)</th>
<th>P Value</th>
<th>Low Dose (N=151)</th>
<th>High Dose (N=157)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC for dyspnea at 72 hr</td>
<td>4456±1468</td>
<td>4699±1573</td>
<td>0.36</td>
<td>4478±1550</td>
<td>4668±1496</td>
<td>0.04</td>
</tr>
<tr>
<td>Freedom from congestion at 72 hr — no./total no. (%)</td>
<td>22/153 (14)</td>
<td>22/144 (15)</td>
<td>0.78</td>
<td>16/143 (11)</td>
<td>28/154 (18)</td>
<td>0.09</td>
</tr>
<tr>
<td>Change in weight at 72 hr — lb</td>
<td>-6.8±7.8</td>
<td>-8.1±10.3</td>
<td>0.20</td>
<td>-6.1±9.5</td>
<td>-8.7±8.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Net fluid loss at 72 hr — ml</td>
<td>4237±3208</td>
<td>4249±3104</td>
<td>0.89</td>
<td>3575±2635</td>
<td>4899±3479</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in NT-proBNP at 72 hr — pg/ml</td>
<td>-1316±4364</td>
<td>-1773±3828</td>
<td>0.44</td>
<td>-1194±4094</td>
<td>-1882±4105</td>
<td>0.06</td>
</tr>
<tr>
<td>Worsening or persistent heart failure — no./total no. (%)</td>
<td>38/154 (25)</td>
<td>34/145 (23)</td>
<td>0.78</td>
<td>38/145 (26)</td>
<td>34/154 (22)</td>
<td>0.40</td>
</tr>
<tr>
<td>Treatment failure — no./total no. (%)↑</td>
<td>59/155 (38)</td>
<td>57/147 (39)</td>
<td>0.88</td>
<td>54/147 (37)</td>
<td>62/155 (40)</td>
<td>0.56</td>
</tr>
<tr>
<td>Increase in creatinine of &gt;0.3 mg/dl within 72 hr — no./total no. (%)</td>
<td>27/155 (17)</td>
<td>28/146 (19)</td>
<td>0.64</td>
<td>20/147 (14)</td>
<td>35/154 (23)</td>
<td>0.04</td>
</tr>
<tr>
<td>Length of stay in hospital — days</td>
<td></td>
<td></td>
<td>0.97</td>
<td></td>
<td></td>
<td>0.55</td>
</tr>
<tr>
<td>Median</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>3–9</td>
<td>3–8</td>
<td>4–9</td>
<td>3–8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive and out of hospital — days</td>
<td></td>
<td></td>
<td>0.36</td>
<td></td>
<td></td>
<td>0.42</td>
</tr>
<tr>
<td>Median</td>
<td>51</td>
<td>51</td>
<td>50</td>
<td>52</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. To convert pounds to kilograms, divide by 2.2. AUC denotes area under the curve, and NT-proBNP N-terminal pro-brain natriuretic peptide.

† Treatment failure was defined as the development of any one of the following during the 72 hours after randomization: increase in serum creatinine level of more than 0.3 mg per deciliter (26.5 μmol per liter), worsening or persistent heart failure, clinical evidence of excessive diuresis requiring intervention (e.g., administration of intravenous fluids), or death.

Kaplan–Meier Curves for the Clinical Composite End Point of Death, Rehospitalization, or Emergency Department Visit.

A Diuretic Protocol Increases Volume Removal and Reduces Readmissions Among Hospitalized Patients With Acute Decompensated Heart Failure

A. Bolus Dosing
- Check BP
  - Systolic < 90 mmHg: Notify physician before giving dose
  - Systolic > 90 mmHg:
    - Give Medication Dose
      - Measure urine output (UO) 2 hrs. after dose is given
      - UO > 250 cc/hr: Notify physician
      - UO > 100 cc/hr and < 250 cc/hr: Check Urine Output 2 hrs. after next dose
        - UO > 250 cc/hr: Notify physician
        - UO > 100 cc/hr and < 250 cc/hr: Max dose? (max = 60 mg Furosemide 4 mg Bumetanide)
        - UO < 100 cc/hr: No
      - UO < 100 cc/hr: Double next dose

B. Continuous Infusion
- Check BP
  - Systolic < 90 mmHg: Notify physician before giving dose
  - Systolic > 90 mmHg:
    - Give Medication Dose
      - Measure urine output (UO) 2 hrs. after dose is given
      - UO > 250 cc/hr: Notify physician
      - UO > 100 cc/hr and < 250 cc/hr: Check Urine Output 2 hrs. after next dose
        - UO > 250 cc/hr: Notify physician
        - UO > 100 cc/hr and < 250 cc/hr: Max dose? (max = 40 mg/hr Furosemide 2 mg/hr Bumetanide)
        - UO < 100 cc/hr: No
      - UO < 100 cc/hr: Double next dose
A Diuretic Protocol Increases Volume Removal and Reduces Readmissions Among Hospitalized Patients With Acute Decompensated Heart Failure
A Diuretic Protocol Increases Volume Removal and Reduces Readmissions Among Hospitalized Patients With Acute Decompensated Heart Failure

[Diagram showing a decision tree for diuretic protocol]
Diuretics in ADHF

Diuretic dose should be 2.5X outpatient dose

Titration should occur at least 2X day to achieve a urine output of 100-250 mL/hr

Continuous infusion = bolus

This should occur until adequate decongestion occurs

This dosing strategy should be compared to other therapies - ULTRAFILTRATION
Why Ultrafiltration (UF)

Usual care does not improve outcomes in ADHF

UF Theoretical advantages

- Isotonic fluid removal (more Na removed)
- Better decongestion
- Decreased risk of electrolyte abnormalities

Inpatient or outpatient

Will lead to sustained hemodynamic and neurohumoral changes
Why Ultrafiltration (UF)

UF theoretical disadvantages

- High cost
- Need for venous access (may be peripheral)
- Anticoagulation
- Availability
- Outcomes
Comparison of sodium removal with various treatment options.

- VRA
- AA1RA
- Diuretics
- Ultrafiltration

Kazory A CJASN 2013;8:1816-1828
Ultrafiltration

- Movement of **Fluid** through a semi permeable membrane caused by pressure gradient (TMP)
- A positive and negative pressure required
Proposed pathophysiologic pathways underlying decompensated heart failure and renal dysfunction.

Kazory A. CJASN 2013;8:1816-1828

©2013 by American Society of Nephrology
TREATMENT OF SEVERE FLUID OVERLOAD BY ULTRAFILTRATION

Marc Eliot Silverstein, M.D., Cheryl A. Ford, B.S., Michael J. Lysaght, M.S.,
and Lee W. Henderson, M.D.
Figure 6. Extracorporeal Circuit for Use of the Ultrafilter in Clinical Setting Other than Extracorporeal Hemodialysis.
Ultrafiltration

Aquadex FlexFlow console

UF 500 blood circuit set

Console cart

Nurse not included
ADHF – Role for Ultrafiltration

Clinical Trials

RAPID – CHF
UNLOAD
CARRESS – HF
AVOID - HF
RCT feasibility trial of UF vs. “usual care” for ADHF

40 patients

Primary outcomes weight loss and volume removed

Trend toward more weight loss in UF group but not statistically significant

“usual care” not defined
Median cumulative fluid removal at 24 and 48 h in patients assigned to ultrafiltration (solid line) and usual care (dashed line). *p = 0.001; **p = 0.012.
From: Ultrafiltration Versus Usual Care for Hospitalized Patients With Heart Failure: The Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure (RAPID-CHF) Trial


Figure Legend:

Median weight loss at 24 and 48 h in patients assigned to ultrafiltration (solid line) and usual care (dashed line).
RCT 200 patients with ADHF to get “usual care” vs. UF

Exclusion – creatinine > 2.9, inability to obtain venous access and hypotension

48 hr wt loss UF > “usual care”

ADHF readmissions UF < “usual care”

“usual care” – not defined

Decongestion not equal
Unload Trial

A

![Graph showing weight loss comparison between Ultrafiltration Arm and Standard Care Arm.]

- **Ultrafiltration Arm**:
  - Mean weight loss: 5.0 kg, CI: 0.68 kg
  - Sample size: N = 83
- **Standard Care Arm**:  
  - Mean weight loss: 3.1 kg, CI: 0.75 kg
  - Sample size: N = 84

- **Statistical Test**: t-test, p = 0.001

B

![Graph showing dyspnea score comparison between Ultrafiltration Arm and Standard Care Arm.]

- **Ultrafiltration Arm**:  
  - Mean dyspnea score: 6.4, CI: 0.11
  - Sample size: N = 80
- **Standard Care Arm**:  
  - Mean dyspnea score: 6.1, CI: 0.15
  - Sample size: N = 83

- **Statistical Test**: t-test, p = 0.35

C

![Graph showing serum creatinine change over time for Ultrafiltration Arm and Standard Care Arm.]

- **Statistical Test**: p > 0.05 at all time points

- **Time Points**: 8 hrs, 24 hrs, 48 hrs, 72 hrs, Discharge, 10 Days, 30 Days, 90 Days
Unload Trial

Percentage of Patients Free From Re-Hospitalization

Days

No. Patients at Risk

Ultrafiltration Arm 88 85 80 77 75 72 70 66 64 64 45
Standard Care Arm 86 83 77 74 66 63 59 58 52 41

p = 0.037
CARRESS – HF

RCT 188 patients ADHF and worsening renal function – UF vs. defined medical care

Exclusion – creatinine > 3.5

Weight loss at 96 hrs same in both groups

GFR declined in UF group

Because of GFR decrease and adverse events study stopped short of goal of 200 patients

RATE OF CLINICAL DECONGESTION 10% (96 hrs)
AT RANDOMIZATION – STEPPED PHARMACOLOGIC CARE ARM

UO > 5 L/day → Reduce current diuretic regimen if desired
UO 3-5 L/day → Continue current diuretic regimen
UO < 3 L/day → See table

<table>
<thead>
<tr>
<th>Current Dose</th>
<th>Suggested Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>loop (/day)</td>
<td>thiazide</td>
</tr>
<tr>
<td></td>
<td>loop (/day)</td>
</tr>
<tr>
<td>A</td>
<td>≤ 80</td>
</tr>
<tr>
<td>B</td>
<td>81-160</td>
</tr>
<tr>
<td>C</td>
<td>161-240</td>
</tr>
<tr>
<td>D</td>
<td>&gt; 240</td>
</tr>
</tbody>
</table>

AT 24 Hrs - STEPPED PHARMACOLOGIC CARE ARM
Persistent Volume Overload Present
UO > 5 L/day → Reduce current diuretic regimen if desired
UO 3-5 L/day → Continue current diuretic regimen
UO < 3 L/day → Advance to next step on table

AT 48 Hrs - STEPPED PHARMACOLOGIC CARE ARM
Persistent Volume Overload Present
UO > 5 L/day → Reduce current diuretic regimen if desired
UO 3-5 L/day → Continue current diuretic regimen
UO < 3 L/day → Advance to next step on table and consider:
Dopamine or dobutamine at 2 ug/kg/hr if SBP < 110 mmHg and EF < 40% or RV systolic dysfunction. Nitroglycerin or Nesiritide if SBP > 120 (any EF) and Severe Symptoms
Changes in Serum Creatinine and Weight at 96 Hours (Bivariate Response).

Ultrafiltration (N=92)

Pharmacologic therapy (N=94)

P=0.003

Changes from Baseline in Serum Creatinine and Body Weight at Various Time Points, According to Treatment Group.

A  Serum Creatinine

B  Body Weight
AVOID - HF

Ongoing RCT with 800 patients – diuretics vs. UF (adjusted)

Time to first HF event within 90 days after discharge. HF events are defined as HF rehospitalization or unscheduled outpatient or emergency room treatment with IV loop diuretics or unscheduled outpatient Aquapheresis treatment.

Diuretics – high dose according to DOSE trial (q12 or drip)

May 2016 Excludes creatinine > 2.9
Unfortunately study stopped by sponsor due to slow enrollment – 224 patients
UF better at weight loss and rehospitalization but not statistically significant
UF worse with serious adverse events related to intervention (cardiac failure, cardiorespiratory arrest, GI bleeding, infections, AKI, dehydration, hyperkalemia, and deep-vein thrombosis) p .026
UF Recommendations

Canada, US and European guidelines

UF *may* be considered as an alternative treatment for ADHF in diuretic resistant patients

Definition of diuretic resistance unclear (< 2500 mL urine output day on titrated loop diuretics?)

UF should be one component of protocolized guideline treatment of ADHF
Case 3

A 65 yo man is admitted with ADHF. He has a high CVP with peripheral edema and ascites. His baseline creatinine is 1.5 mg/dl. His admission creatinine is 3.0 mg/dl. He is placed on ultrafiltration (UF) by the heart failure team. His BNP is 4000.
| Congestion | | |
| --- | --- | |
| | - | + |
| Adequate perfusion | + | Dry and warm | Wet and warm |
| | | Orthopnea, rales | Orthopnea, rales |
| | | Abnormal valsalva | Abnormal valsalva |
| | | ↓ Jugular venous pressure | ↓ Jugular venous pressure |
| | | Abdominojugular reflux | Abdominojugular reflux |
| | | Hepatomegaly | Hepatomegaly |
| - | Dry and cold | Wet and cold |
| | ↓ Pulse pressure | Heptatomegaly |
| | Cool extremities | Ascites |
| | Altered mentation | Edema |
| | Worsening renal function | |

Table 1 Clinical assessment of acute heart failure syndromes, adapted and modified [3]
ADHF – Treatment (warm and wet)

2.5X home diuretics and give IV q6. Reassess in 6-12 hours

If UO adequate – continue. If not – double diuretics. Reassess in 6-12 hours

If UO adequate – continue. If not – continuous loop diuretic. Reassess in 6-12 hours

If UO adequate – continue. If not – DIURETIC RESISTANT

UO adequacy 150 ml/hr or 2500 ml/day
ADHF - Treatment (cold and wet)

1. If SBP < 90, add pressors, mechanical support and inotropes
2. Use diuretic protocol
ADHF – Treatment (diuretic resistant)

Measure IAP

If > 8mm, do abdominal US.
If US shows ascites, tap to IAP of < 8
If no ascites, consider alternative treatments
If < 8, consider for alternative treatments

Alternative treatment – ultrafiltration, dialysis, inotropes, combination diuretics, vasodilators, and ADH antagonists (if hyponatremic)