Opportunities to Harness Technology to Improve Blood Pressure and Volume Management in Maintenance Dialysis

Manfred Hecking, MD PhD
Assoc. Prof. of Medicine, Nephrology, Medical University of Vienna, Austria

Group 3 members kindly provided edits and support:

Martin Gallagher, Magdalena Madero, Maria Rosa Costanzo, Andrew Davenport, Simon Davies, Vivek Jha, Jay R Lacson, Charmaine Lok, Fabio Paglialonga, Roberto Pecoits-Filho, Laura Sola
DISCLOSURES

• Speaker Honoraria from Fresenius Medical Care: 2018: Symposium on Intensive Care in Pörtschach, Austria - “Fluid “ - (€ 900,00); 2017: Chairman, Scientific Symposium at ERA-EDTA in Madrid – “Orchestrating Electrolytes” - (€ 900,00); 2016: Meeting for Chinese Delegates at the ERA-EDTA in Vienna - Hemodiafiltration: “Clinical Aspects, Personal Opinion, Perspective in ESRD Care” - (€ 900,00)
• Speaker Honoraria from Astellas Pharma: 2016: Feldkirch, Austria; Salzburg, Austria, Innsbruck, Austria “Management of posttransplant diabetes” (€ 1800,00)
• Research grant from Boehringer Ingelheim: “EMPaglirozin and RAs in Kidney Disease ” (€ 321.935,00), clinicaltrials.gov: NCT03078101
• Research grant from Astellas Pharma and Eli/Lilly: “Early insulin therapy for prevention of posttransplant diabetes” (€ 154.170,00, € 33.000,00), “ITP-NODAT study”, clinicaltrials.gov: NCT03507829
• Research grant from Astellas Pharma: “Sensor-Augmented Insulin Pump Therapy against Post-transplant Hyperglycemia: A Semi-Closed Loop System to Prevent New-Onset Diabetes after Renal Transplantation” (€ 42.825,00), “SAPT-NODAT study”, clinicaltrials.gov: NCT01680185
• Research grant from Astellas Pharma: “Treat-to-target trial of basal insulin in post-transplant hyperglycemia (TIP): efficacy and safety of a novel protocol in renal transplant recipients receiving a tacrolimus-based immunosuppression” (€ 49.500,00), “TIP-study”, clinicaltrials.gov: NCT00830297
• Research grant from Nikkiso Co LTD: “Response Options to Blood Volume Monitoring in Fluid Overloaded Hemodialysis Patients” (€ 20.000,00), “BVM-Reg study”, clinicaltrials.gov: NCT01416753
• Competitive Academic Funding: Austrian Science Fund (FWF), NIH/NIDDK, Anniversary Fund of the Austrian National Bank (OeNB), Else Kröner-Fresenius Foundation
Thomson et al., *Arch Intern Med* 120: 153–167, 1967:
Reduction of blood pressure to hypotensive levels during ultrafiltration

Henderson, 1980:
Weight obtained at the conclusion of a regular dialysis treatment below which the patient more often than not will become symptomatic and go into shock.

Charra et al., *Nephrol Dial Transplant* 11[Suppl 2]: 16–19, 1996:
Body weight at the end of dialysis at which the patient can remain normotensive until the next dialysis despite the retention of saline and ideally without the use of antihypertensive medications

Raimann et al., 2008:
Defined by continuous calf bioimpedance analysis during dialysis. Dry-weight = flattening of the baseline/instantaneous impedance ratio curve for at least 20 minutes in the presence of ongoing ultrafiltration

A combination of subjective and objective measurements

“CONTROVERSIS CONFERENCE”... 1st CONTROVERSY MAY BE BLOOD PRESSURE:

Wabel P et al., Nephrol Dial Transplant 2008; Sep;23(9): 2965-71


Dekker M et al., Nephrol Dial Transplant 2018; Nov 1;33(11):2027-2034
WHAT DOES BLOOD PRESSURE DEPEND ON?

- **Q=cardiac output over 1 min**, a function of:
  - stroke volume
  - Preload
  - Inotropy
  - Afterload

- **SVR=systemic vascular resistance**


---

**TABLE III**

| Sodium and Potassium in the Arteriolar Wall of Various Normotensive and Hypertensive Rats |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| (mEq/100 g dry tissue)         | 25 Normal rats (A)              | p Value of the difference | 30 Rats with *cured* hypertension (B) | p Value of the difference |
|                                | 25 Rats with continuing hypertension (C) |
| Na                              | 22.1 ± 0.4                      | 0.03                         | 23.5 ± 0.5                      | 0.00006                        | 27.3 ± 0.7                      |
| K                               | 21.2 ± 0.3                      | >0.5                         | 21.2 ± 0.3                      | 0.3                            | 21.7 ± 0.4                      |
| Cl                              | 21.5 ± 0.8                      | 0.5                          | 22.3 ± 0.7                      | 0.08                           | 24.3 ± 0.9                      |
| Na + K (mEq/100 g dry tissue)   | 43.3 ± 0.6                      | 0.14                         | 44.6 ± 0.7                      | 0.0004                         | 49.0 ± 1.0                      |
| Arterial pressure before clip removal (mm Hg) | 126 (101-140)             | 197                           | 202 (158-250)                   |                                |
| Arterial pressure one week after clip removal or sham operation (mm Hg) | 125 (100-141)             | 0.02                          | 132 (111-152)                   | 197                            |

* ± Indicates the standard error of the mean.  
† Mean and range.
ONE STEP BACK: ON VOLUME & TECHNOLOGIES (1) FOR VOLUME [DRY WEIGHT] ASSESSMENT; (2) FOR VOLUME MANAGEMENT

Terminology: Water (Hydration) versus Isotonic Fluid (Volume through ‘salt’ + water)
FLUID VOLUME ASSESSMENT

• Total Body Volume* (=TBV, =TBW)
• Intracellular Volume* (=ICV, =ICW)
• Extracellular Volume* (=ECV, =ECW)
• Total Blood Volume* (=TBV, =TBW)

*Gold Standards:
• Total Body Volume: Deuterium (D$_2$O) Dilution
• Intracellular Volume: ICV$_{TBK}$ = Total Body Potassium (TBK)/152 [intracellular K = 152 mmol/L]
• Extracellular Volume: Sodium bromide (NaBr) Dilution
• Total Blood Volume: $^{131}$I-labeled albumin + $^{51}$Cr-labeled red cells → Indocyanine Green

Moissl U et al., Physiol Meas 2006 Sep;27(9):921-33
On the Importance of Pedal Edema in Hemodialysis Patients

- Pedal Edema
- Chest X-ray
- Inferior Vena Cava Diameter
- Lung Comets
- (Diagnostic) Relative Blood Volume Monitoring
- Echocardiography
- Pulse Pressure

...in 2 papers only

Inferior vena cava diameter, blood volume monitoring, plasma volume markers, and inflammation markers were not determinants of edema.


Lung Congestion as a Risk Factor in End-Stage Renal Disease

[... “patients with very severe congestion had a 4.2-fold risk of death (HR=4.20, 95% CI=2.45-7.23) [... adjusted for NYHA class and other risk factors”

Zoccali C et al., Blood Purif. 2013;36(3-4):184-91
FLUID VOLUME ASSESSMENT

• (Diagnostic) Relative Blood Volume Monitoring
  • Prognostic Importance

Agarwal R et al., Hypertension.
2010 Sep;56(3):512-7

• (Diagnostic) Relative Blood Volume Monitoring
  • Practical Relevance

Relative Plasma Volume Monitoring During Hemodialysis Aids the Assessment of Dry Weight
Arjun D. Sinha, Robert P. Light and Rajiv Agarwal

Hypertension. 2010 Feb;55(2):305-11
**FLUID VOLUME ASSESSMENT**

FROM HERE (TOTAL VOLUMES)

TO THERE (HOW MUCH IS TOO MUCH)

**Gold Standards:**

- **Total Body Volume:** Deuterium ($D_2O$) Dilution
- **Intracellular Volume:** $ICV_{TBK} = \frac{Total\ Body\ Potassium\ (TBK)}{152}$ [intracellular $K = 152$ mmol/L]
- **Extracellular Volume:** Sodium bromide ($NaBr$) Dilution

Body fluid volume determination via body composition spectroscopy in health and disease

TBW $D_2O = ECW NaBr + ICW TBK$

ECW $NaBr = TBW D_2O - ICW TBK$

*Moissl U et al., Physiol Meas 2006 Sep;27(9):921-33*
FLUID VOLUME ASSESSMENT

Assessment of Extracellular Fluid Volume and Fluid Status in Hemodialysis Patients: Current Status and Technical Advances

Direct Current → Resistance

Alternating Current → Resistance & Reactance

Cole Model
- From 50 phase angles to Capacitance and
- Resistance E
- Resistance I

Hanai Model
- From RE and RI to ECV und ICV

FLUID VOLUME ASSESSMENT

A whole-body model to distinguish excess fluid from the hydration of major body tissues

### FLUID VOLUME & OUTCOMES

- Bioimpedance Spectroscopy in ESRD (PD and HD)
  - Prognostic Importance

#### Study or Subgroup | Weight | IV, Random, 95% CI
---|---|---
3.1.1 Phase Angle (PA) – For every 1 degree decrease in PA
Beberashvili 2014a | 39.2% | 1.64 [1.42, 1.90]
Beberashvili 2014b | 24.8% | 1.33 [0.96, 1.85]
Koh 2011 | 21.8% | 2.56 [1.76, 3.73]
Shin 2017 | 14.3% | 1.79 [1.05, 3.03]
**Subtotal (95% CI)** | 100.0% | 1.74 [1.37, 2.21]
Heterogeneity: Tau² = 0.03; Chi² = 7.03, df = 3 (P = 0.07); I² = 57% Test for overall effect: Z = 4.49 (P < 0.00001)

3.1.2 Overhydration Index – cut off of OH > 15%
Caetano 2016 | 12.9% | 2.22 [1.30, 3.80]
Chazot 2012 | 10.4% | 3.41 [1.62, 7.17]
Dekker 2017 | 16.3% | 2.62 [2.08, 3.30]
Drepper 2016 | 5.6% | 7.82 [2.10, 29.07]
Kim 2015 | 9.8% | 2.58 [1.16, 5.74]
Onofriescu 2015 | 13.2% | 1.87 [1.12, 3.13]
Wizemann 2009 | 14.4% | 2.10 [1.39, 3.18]
Zoccalli 2017 | 17.3% | 1.26 [1.19, 1.33]
**Subtotal (95% CI)** | 100.0% | 2.26 [1.56, 3.34]
Heterogeneity: Tau² = 0.22; Chi² = 62.53, df = 7 (P < 0.00001); I² = 89% Test for overall effect: Z = 4.27 (P < 0.00001)

#### For the Body Composition Monitor:
- 9 RCTs with BCM only
  - 2156 patients (HD + PD)
- 38 non-RCTs with BCM
  - 104,892 patients (HD, PD, CKD)

(only studies with >100 patients and reporting cardiovascular outcomes) (some patients are included twice)

P. Wabel, personal communication

## Fluid Volume & Outcomes

- Bioimpedance Spectroscopy in ESRD (PD only)
- Prognostic Importance

### Study

<table>
<thead>
<tr>
<th>ID</th>
<th>RR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality-ECW/TBW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O’Lone EL, 2014</td>
<td>2.05 (1.31, 3.22)</td>
<td>46.55</td>
</tr>
<tr>
<td>Guo Q, 2015</td>
<td>13.58 (1.08, 170.11)</td>
<td>1.57</td>
</tr>
<tr>
<td>Kang SH, 2016</td>
<td>2.19 (1.43, 3.34)</td>
<td>51.88</td>
</tr>
<tr>
<td>Subtotal ($I^2 = 3.9%, p = 0.353$)</td>
<td>2.19 (1.59, 3.00)</td>
<td>100.00</td>
</tr>
<tr>
<td>Technique failure-ECW/TBW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jones CH, 2004</td>
<td>6.13 (4.78, 7.48)</td>
<td>98.54</td>
</tr>
<tr>
<td>Guo Q, 2015</td>
<td>13.33 (2.12, 83.68)</td>
<td>1.46</td>
</tr>
<tr>
<td>Subtotal ($I^2 = 0.0%, p = 0.411$)</td>
<td>6.20 (4.96, 7.74)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Note: weights are from random effects analysis.
**BIOIMPEDANCE SPECTROSCOPY & OUTCOMES**

**WHICH PREDICTORS?**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.1.1 Phase Angle (PA)</strong> – For every 1 degree decrease in PA</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3.1.2 Overhydration Index – cut off of OH &gt; 15%</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**All-cause mortality - ECW/TBW**

- Vector length
- Phase angle
- ECW/TBW
- ECW volume
- OH index

**Hypertensive hypervolemic man**

**Clinically normovolemic woman**

**Davies SJ & Davenport A, Kidney Int 2014 Sep;86(3):489-96**


**Shu Y et al., Blood Purif. 2018; 46(4):350-358**
FLUID VOLUME ASSESSMENT

- Bioimpedance and...
- Pedal Edema
- Chest X-ray
- Inferior Vena Cava Diameter
- Biochemical Markers
- Lung Comets
- (Diagnostic) Relative Blood Volume Monitoring
- Dual-energy X-ray absorptiometry (=DXA)
- Magnetic Resonance Imaging (MRI)
- Echocardiography
- Pulmonary Artery Pressure
- Pulse Pressure
- Stroke Volume Variation
- Leg Raising Test
- Blood Pressure

Keane DF et al., ASAIO J. 2018 Nov/Dec;64(6):812-818

Do pre-haemodialysis estimates of extracellular volume excess using bioimpedance and N terminal brain natriuretic peptide correlate with cardiac chamber size measured by magnetic resonance imaging?

Yoowannakul MD et al., Ther Apher Dial. 2018 Nov 23

Comparison of Multifrequency Bioelectrical Impedance Analysis and Dual-Energy X-ray Absorptiometry Assessments in Outpatient Hemodialysis Patients


Predicting mortality in haemodialysis patients: a comparison between lung ultrasonography, bioimpedance data and echocardiography parameters

Fluid Overload and BMI inversely associated: Explanation for 'Reverse Epidemiology'? 


The Effect of Racial Origin on Total Body Water Volume in Peritoneal Dialysis Patients 


Impact of fluid status and inflammation and their interaction on survival: a study in an international hemodialysis patient cohort 

Marijke J.E. Dekker1,2, Daniele Marcelli3, Bernard J. Cauad3, Paola Carioni3, Yuedong Wang4, Aileen Grassmann3, Constantijn J.A.M. Konings5, Peter Kotanko2, Karel M. Leunissen1, Nathan W. Levin1, Frank M. van der Sande1, Xiaoling Ye3, Vaibhav Maheshwari2, Len A. Usyvat5,7 and Jeroen P. Kooman1, for the MONDO Initiative
### Tools to assess fluid status

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staff involvement</strong></td>
<td>High</td>
<td>High</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Time requirement</strong></td>
<td>Medium</td>
<td>High</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td><strong>System costs</strong></td>
<td>Medium</td>
<td>High</td>
<td>Medium</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Between observer variability</strong></td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Within observer variability</strong></td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Invasiveness/inconvenience</strong></td>
<td>Medium</td>
<td>High</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Assessment frequency</strong></td>
<td>Medium</td>
<td>Low</td>
<td>Medium</td>
<td>Medium</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td><strong>Correlation with fluid status</strong></td>
<td>Medium</td>
<td>High</td>
<td>High</td>
<td>Medium</td>
<td>Medium</td>
<td>?</td>
</tr>
<tr>
<td><strong>Direct / indirect marker</strong></td>
<td>Indirect</td>
<td>Direct</td>
<td>Direct</td>
<td>Indirect</td>
<td>Indirect</td>
<td>Direct</td>
</tr>
<tr>
<td><strong>Measurement Accuracy</strong></td>
<td>Medium</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>?</td>
</tr>
<tr>
<td><strong>Suitable for ...</strong></td>
<td>HD &amp; PD</td>
<td>HD &amp; PD</td>
<td>HD &amp; PD</td>
<td>HD &amp; PD</td>
<td>HD</td>
<td>HD</td>
</tr>
</tbody>
</table>

---

**Summary 1: Harnessing Technology To Assess Volume [Dry Weight]**

- **Ultra-sound (lung; IVC)**
- **Tracers**
- **Bio-impedance**
- **Bio-markers**
- **Relative blood volume**
- **Absolute blood volume (experimental)**
- **Staff involvement**: High High Medium Low Low Low
- **Time requirement**: Medium High Medium Low Low Low
- **System costs**: Medium High Medium Medium Low Low Low
- **Between observer variability**: High Low Low Low Low Low
- **Within observer variability**: Medium Low Low Low Low Low
- **Invasiveness/inconvenience**: Medium High Medium Low Low Low
- **Assessment frequency**: Medium Low Medium Medium High High
- **Correlation with fluid status**: Medium High High Medium Medium ?
- **Direct / indirect marker**: Indirect Direct Direct Indirect Indirect Direct
- **Measurement Accuracy**: Medium High High High High ?
- **Suitable for ...**: HD & PD HD & PD HD & PD HD & PD HD HD

---

**Courtesy Peter Kotanko**

INTRADIALYTIC VOLUME MANAGEMENT: HF/HDF VS HD (‘HOT TOPIC’)

- **High-flux HD** with unknown convective removal
  - Blood: 300 → 510
  - Ultrapure dialysis fluids: 300 → 550
  - 290 → 500
  - Substitution fluid from bag: 290 → 40

- **Classical HDF** with 50 ml/min convective removal
  - Blood: 300 → 510
  - Ultrapure dialysis fluid: 500 → 420
  - 40

- **On-line HDF** with 90 ml/min convective removal
  - Blood: 300 → 510
  - Ultrapure dialysis fluid: 420 → 500
  - 50

NDT Plus 2010; 3: 8-16

Courtesy Peter J. Blankestijn

KDIGO
Intradialytic Volume Management: Cooling

According to the original observation by Maggio et al. [19] that dialysate temperature set at about 35°C affords a better haemodynamic stability than the standard dialysate temperature of 37–38°C, an alternative hypothesis to explain the reduction of hypotension episodes during online HDF is suggested by Donauer et al. [20], who identified blood cooling as the main blood pressure-stabilizing factor in online HDF. During online HDF, an enhanced energy loss within the extracorporeal system occurred, despite identical temperature settings for dialysate and substitution fluids. As a result, the blood returning to the patient was cooler during online HDF than during HD. Moreover, the mean blood temperature was lower in online HDF, even in the patient’s circulation, and blood volume was significantly more reduced. The incidence of symptomatic hypotension was similar to that of online HDF by using cooler temperature-controlled HD.

Beneficial Effect of HDF, Low Temp HD, (and Iso-UF): Explained by Cooling/Energy Transfer

Energy Transfer Is the Single Most Important Factor for the Difference in Vascular Response between Isolated Ultrafiltration and Hemodialysis

Frank M. van der Sande, Ulrich Gladziwa, Jeroen P. Koeman, George Böcker, and Karel M. L. Leunissen

Department of Internal Medicine and Nephrology, University Hospital Maastricht, The Netherlands; and University of Witten/Herdecke, Germany.

Reduction of hypotensive side effects during online-haemodialfiltration and low temperature haemodialysis

Johannes Donauer, Christoph Schweiger, Brigitta Rumberger, Bernd Krummle, and Joachim Böhler

1Department of Nephrology, University Hospital Freiburg and 2Deutsche Klinik für Diagnostik, Division of Nephrology, Wiesbaden, Germany.


Courtesy Thomas Roy
From Isolated Ultrafiltration to Blood-Temperature-Controlled Feedback: An Odyssey Started by Jonas Bergström

Jeroen P. Kooman a, Frank van der Sande a, Karel Leunissen a, Stanley Shaldon b

a University Hospital Maastricht, Maastricht, The Netherlands;
b 25 Le Michelangelo 7, Avenue des Papalins, Monaco, Monte Carlo

It is tempting to read, in the commentary of Jonas Bergström himself, that the improved haemodynamic stability during isolated ultrafiltration was actually discovered in 1973 by a technical fault of the dialysis module, which had been in bypass position without alarming, meaning that no dialysate had passed during the treatment. During this faulty treatment, fluid removal was remarkably well tolerated in a patient who used to experience symptomatic hypotension during every treatment. Due to Bergström’s combination of clinical and scientific interest, this single observation was translated into a structured research program. The paper published in the...
**Table 3.** Individual values for changes in FVR, VT and HR

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dialysate temperature: 37.5°C</th>
<th>Dialysate temperature: 35.0°C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FVR</td>
<td>VT</td>
</tr>
<tr>
<td></td>
<td>UF</td>
<td>HD</td>
</tr>
<tr>
<td>1</td>
<td>+731</td>
<td>+177</td>
</tr>
<tr>
<td>2</td>
<td>+1372</td>
<td>+180</td>
</tr>
<tr>
<td>3</td>
<td>+3671</td>
<td>-1983</td>
</tr>
<tr>
<td>4</td>
<td>+1058</td>
<td>-164</td>
</tr>
<tr>
<td>5</td>
<td>+1221</td>
<td>-625</td>
</tr>
<tr>
<td>6</td>
<td>+577</td>
<td>-266</td>
</tr>
<tr>
<td>7</td>
<td>+613</td>
<td>-320</td>
</tr>
<tr>
<td>8</td>
<td>+273</td>
<td>+471</td>
</tr>
<tr>
<td>9</td>
<td>+1537</td>
<td>+202</td>
</tr>
<tr>
<td>10</td>
<td>+1079</td>
<td>+283</td>
</tr>
<tr>
<td>11</td>
<td>+534</td>
<td>+2181</td>
</tr>
<tr>
<td>12</td>
<td>+1435</td>
<td>+249</td>
</tr>
</tbody>
</table>

FVR (mmHg/ml/100 ml/s); VT (mmHg/ml/100 ml); HR (beats/min). Patients 1–6 UF–HD; patients 7–12 HD–UF.

**Conclusions.** We conclude that differences in cardio-vascular reactivity between isolated ultrafiltration and combined ultrafiltration–haemodialysis are only partially explained by differences in the extracorporeal blood temperature. In addition, especially venous reactivity is improved by lowering the dialysate temperature.

**Intradialytic Volume Management:**

**Isolated UltraFiltration**

Vascular reactivity during haemodialysis and isolated ultrafiltration: thermal influences

VanKuijk WHM et al., Nephrol Dial Transplant 1995 10:1852-58

![Pictures shown with permission](image-url)
INTRADIALYTIC VOLUME MANAGEMENT:

DIALYSATE COMPOSITION

SODIUM

SODIUM PROFILES

(NA-MODELLING)

Covered by other group

Salt, the Neglected Silent Killer
Stanley Shaldon* and Joerg Vienken†

The Evils of Intradialytic Sodium Loading
Stephan Thijsse‡, Jochen G. Raimann‡, Len A. Usvyat§, Nathan W. Levin‡, Peter Kotanko‡

BMC Nephrology 2006, 7:7
DOI: 10.1186/1471-2369-7-7

Salt – A Potential ‘Uremic Toxin’?
Eberhard Ritz, Ralf Dikow, Christian Morath, Vedat Schwenger

Department of Internal Medicine, Ruperto Carola University Heidelberg, Heidelberg, Germany

No time – will be discussed in group 3
Intradialytic Volume Management: Ultrafiltration Rate Profiles

Relative Blood Volume-Controlled Feedback of the Ultrafiltration Rate

Constant UFR
Stepwise UFR profile
“Auto-UFR”

One Patient, 2 Subsequent Treatments

“The actual ultrafiltration rate is the maximum ultrafiltration rate multiplied by a variable known as the ultrafiltration coefficient (ranging from zero to one). At the beginning of HD, the ultrafiltration coefficient equals one until the relative blood volume is halfway towards the critical relative blood volume. Once past the halfway point, the ultrafiltration coefficient decreases linearly (thus slowing the actual ultrafiltration rate) until the critical relative blood volume is reached, when the coefficient equals zero to effectively stop ultrafiltration.”
**Intradialytic Volume Management: A Case for Absolute Blood Volume Measurements?**

**Feedback Control in Hemodialysis—Much Ado about Nothing?**


<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with IME</td>
<td>24</td>
<td>3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frequency of all IME (%)</td>
<td>66 (12.2)</td>
<td>5 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptomatic hypotension</td>
<td>47</td>
<td>3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cramps</td>
<td>16</td>
<td>2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Loss of voice</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Gold Standard:*
- **Total Blood Volume**: $^{131}$I-labeled albumin + $^{51}$Cr-labeled red cells; Indocyanine Green

Absolute blood volume*: measured by dialysate dilution

Target weight was increased or decreased in 32 patients.


* [...] “the futility to controlling intravascular volume using relative changes can be compared with a room thermostat controlling the temperature change rather than the absolute room temperature: the resulting temperature could be anything.”

**Total body volume by bioimpedance**

**Total blood volume by dilution method**

Kron S et al., *ASAIO J.* 2018 Nov/Dec;64(6): 697-700
INTRADIALYTIC VOLUME MANAGEMENT: SEVERAL TECHNIQUES COMBINED

Is the Dry Weight ‘Reducable’? Can Technology Help?
Blood volume-monitored regulation of ultrafiltration in fluid-overloaded hemodialysis patients

Percent of HD-sessions

0.003
0.60
0.03

<table>
<thead>
<tr>
<th>Facility level practices</th>
<th>All facilities (n = 273)</th>
<th>Australia/New Zealand (n = 14)</th>
<th>Canada (n = 18)</th>
<th>Europe (n = 120)</th>
<th>Japan (n = 58)</th>
<th>US (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fluid Volume Management</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol that specifies how often to assess dry weight in most pat's</td>
<td>67 (25%)</td>
<td>4 (29%)</td>
<td>1 (6%)</td>
<td>28 (23%)</td>
<td>26 (46%)</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>Routine orthostatic BP measurement to assess dry weight</td>
<td>157 (58%)</td>
<td>11 (79%)</td>
<td>14 (78%)</td>
<td>55 (46%)</td>
<td>29 (51%)</td>
<td>48 (76%)</td>
</tr>
<tr>
<td>Routine on-line volume indicator to assess dry weight</td>
<td>57 (21%)</td>
<td>2 (15%)</td>
<td>6 (33%)</td>
<td>35 (30%)</td>
<td>3 (5%)</td>
<td>11 (18%)</td>
</tr>
<tr>
<td>Routine bio-impedance study to assess dry weight</td>
<td>13 (5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>11 (9%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Routine on-line volume indicator AND bio-impedance study</td>
<td>6 (2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>5 (4%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Policy that limits fluid removal during dialysis session</td>
<td>93 (35%)</td>
<td>6 (43%)</td>
<td>5 (28%)</td>
<td>44 (37%)</td>
<td>20 (36%)</td>
<td>18 (29%)</td>
</tr>
<tr>
<td>Performs isolated ultrafiltration</td>
<td>192 (73%)</td>
<td>9 (69%)</td>
<td>14 (82%)</td>
<td>95 (80%)</td>
<td>32 (56%)</td>
<td>42 (71%)</td>
</tr>
<tr>
<td><strong>Management of IntraDialytic Hypotension</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol for managing IDH</td>
<td>128 (50%)</td>
<td>8 (57%)</td>
<td>10 (56%)</td>
<td>48 (45%)</td>
<td>23 (40%)</td>
<td>39 (66%)</td>
</tr>
<tr>
<td>Routine sodium modeling/profiling to limit or prevent IDH</td>
<td>118 (43%)</td>
<td>1 (7%)</td>
<td>16 (89%)</td>
<td>53 (44%)</td>
<td>5 (9%)</td>
<td>43 (68%)</td>
</tr>
<tr>
<td>Routine lower dialysate temperature to limit or prevent IDH</td>
<td>128 (47%)</td>
<td>6 (46%)</td>
<td>14 (78%)</td>
<td>73 (61%)</td>
<td>6 (11%)</td>
<td>29 (46%)</td>
</tr>
</tbody>
</table>

ANOTHER WAY OF HARNESING TECHNOLOGY:
STRATEGY OF VOLUME MANAGEMENT (DIALYSIS PLANNING)

One-Year, Single Center Experience

US: From Data Analysis to Policy

Adverse events*

Flythe J et al., Kidney Int. 2011 Jan;79(2):250-7

Disentangling the Ultrafiltration Rate–Mortality Association: The Respective Roles of Session Length and Weight Gain

Fluid Management: The Challenge of Defining Standards of Care

Associations of Posthemodialysis Weights above and below Target Weight with All-Cause and Cardiovascular Mortality
Flythe J et al., Clin J Am Soc Nephrol. 2015 May 7;10(5):808-16

Failed Target Weight Achievement Associates with Short-Term Hospital Encounters among Individuals Receiving Maintenance Hemodialysis

Machek P et al., Nephrol Dial Transplant 2010; 25: 538-44

Ultrafiltration Rates and the Quality Incentive Program: Proposed Measure Definitions and Their Potential Dialysis Facility Implications
ANOTHER WAY OF HARNESING TECHNOLOGY: STRATEGY OF VOLUME MANAGEMENT (DIALYSIS PLANNING)

[...] “the interest in fluid management in the United States has taken root in the last 5 years. The two largest United States dialysis providers recently implemented fluid management clinical programs. In 2013, DaVita launched FluidWise, [...] In late 2016, Fresenius Medical Care, North America released the Fluid Management Dashboard, [...] that identifies patients with postdialysis weights ≥1 kg above or below their prescribed target weight and patients with ultrafiltration rates >13 ml/h per 1 kg in >30% of recent treatments.”


In the US, IDWG remains one of the most important parameters....
**Strategy of Volume Management:**

*Fluid Overload and IDWG are Not the Same*

**Diagram Explanation:**

- **Fluid Retention**
  - Interdialytic Weight Gain
  - Fluid Overload

**Graph Details:**

- **Patient Weight**
  - Predialysis
  - Postdialysis
  - Volume Overload
  - Weight Gain (IDWG)

** KDIGO**

**Volume Overload in Dialysis:**

*The Elephant in the Room, No One Can See*

**References:**

- Kalantar-Zadeh, Circulation 2009
- Wizemann, NDT 2009

**Interdialytic weight gain and fluid overload are two different measures.**

**Courtesy Volker Wizemann: Heidelberger Dialyseseminar 2010**
**Principal Message:**
Greater FO and smaller IDWG predict mortality…

Dehydrated Patients may drink the most.

Cubic spline models estimating multivariate adjusted hazard ratios relative to the IDWG concentration in the second FO quartile (IDWG=0.06). FO quartiles were calculated based on longitudinal means over all measures of a patient during the follow-up. Hazards ratios for IDWG in FO quartiles 1, 3 and 4 were multiplied by the marginal hazard ratios of the FO quartile relative to the second FO quartile.

DOES FLUID VOLUME ASSESSMENT, INTRADIALYTIC VOLUME MANAGEMENT, STRATEGIC VOLUME MANAGEMENT (DIALYSIS PLANING) IMPROVE OUTCOMES?

FLUID VOLUME ASSESSMENT (BY BIOIMPEDANCE)

Covic A et al., Int Urol Nephrol. 2017 Dec;49(12):2231-2245

**Fig. 4** Forest plot for change in overhydration (L)

**Fig. 7** Forest plot the effect on arterial stiffness (pulse wave velocity in m/s)
BIA-based interventions for correction of overhydration have little to no effect on all-cause mortality, whereas BIA improved systolic blood pressure control. Our results should be interpreted with caution as the size and power of the included studies are low. Further studies, larger or with a longer follow-up period, should be performed.”
Recent findings
Eight trials (published 2010–2018) and two meta-analyses (2017) are reviewed.

Summary
The usefulness of bioimpedance spectroscopy in guiding fluid management in dialysis patients is not yet clear. **Bioimpedance can drive clinical decisions that lead to significant changes in fluid status but the best way to apply this in clinical practice requires further studies.**

"The potential benefits of convective modalities over standard HD for cardiovascular outcomes and mortality remain unproved. Further high-quality randomized trials are needed to define the impact of these modalities on clinically important outcomes."

**Does Fluid Volume Assessment, Intradialytic Volume Management, Strategic Volume Management (Dialysis Planning) Improve Outcomes?**

**Intradialytic Volume Management: HemoFiltration / HemoDiaFiltration**

**Outcomes**
- Mortality
- Hospitalizations
- Intradialytic Hypotension
- Biochemical Markers
- Body Mass Index

**Santoro A et al., Am J Kidney Dis. 2008 Sep;52(3):507-18**


**Schiff H et al., Int Urol Nephrol. 2013 Oct;45(5):1389-96**


[“CONTRAST”]

**Locatelli F, Blood Purif. 2015; 40 Suppl 1:24-9**

**Hemofiltration better**

**Hemodiafiltration better**

**Hemodiafiltration better**

**Hemodiafiltration better**

**Hemodiafiltration better**

**No difference**

**Table 2. Randomized clinical studies evaluating the role of HDF on dialysis tolerance.**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Treatments</th>
<th>Patients</th>
<th>Sample Size</th>
<th>Relative risk reduction, %</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locatelli et al. [8], 1996</td>
<td>randomized, prospective</td>
<td>Cuprohane HD</td>
<td>132</td>
<td>380</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low-flux HD</td>
<td>147</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>High-flux HD</td>
<td>51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HDF</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altieri et al. [30], 2004</td>
<td>randomized, crossover, prospective</td>
<td>HF</td>
<td>39</td>
<td>54.5</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HDF</td>
<td>76</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schiff [31], 2007</td>
<td>randomized, crossover, prospective, secondary analysis</td>
<td>High-flux HD HDF</td>
<td>76</td>
<td>152</td>
<td>63.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Locatelli et al. [21], 2010</td>
<td>randomized, prospective</td>
<td>Low-flux HD Online HF Online HDF</td>
<td>70</td>
<td>146</td>
<td>50</td>
<td>0.001</td>
</tr>
<tr>
<td>Maduell et al. [22], 2013</td>
<td>randomized, prospective, secondary analysis</td>
<td>High-flux HD HDF</td>
<td>456</td>
<td>906</td>
<td>28</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**IDH not analyzed**
Does Fluid Volume Assessment, Intradialytic Volume Management, Strategic Volume Management (Dialysis Planing) Improve Outcomes? Intradialytic Volume Management: Cooling/"Thermoneutrality" Against IDH

Selby NM & McIntyre CW, Nephrol Dial Transplant. 2006 Jul;21(7):1883-98

Fixed Temperature Reduction and Body Temperature Monitor better
Does fluid volume assessment, intradialytic volume management, strategic volume management (dialysis planning) improve outcomes? Intradialytic volume management: ISO-UF against IDH

No Meta-Analyses Identified
Isolated Ultrafiltration better (only older studies)
**Does Fluid Volume Assessment, Intradialytic Volume Management, Strategic Volume Management (Dialysis Planning) Improve Outcomes?**

Sodium Concentration in the Dialysate – Sodium Modelling

I am “not allowed” to comment, and there certainly is no time

Be Aware of Bias(!!!!) and Inadequate Na-Delivery when Interpreting any Study
DOES FLUID VOLUME ASSESSMENT, INTRADIALYTIC VOLUME MANAGEMENT, STRATEGIC VOLUME MANAGEMENT (DIALYSIS PLANNING) IMPROVE OUTCOMES?

RELATIVE BLOOD VOLUME-CONTROLLED FEEDBACK OF THE ULTRAFILTRATION RATE

“The adjusted risk ratio for non–access-related and access-related hospitalization was 1.61 (95% confidence interval 1.15 to 2.25; P = 0.01) and 1.52 (95% confidence interval 1.02 to 2.28; P = 0.04) for the Crit-Line monitoring group. Mortality was 8.7% in the Crit-Line monitoring group and 3.3% in the conventional group (P = 0.021).”


Leung et al.: No Difference Meta-Analysis (Nesrallah et al., NDT 2013) not considered because Sodium Conductivity was also adjusted
We computed the cumulative, theoretical 1-month fluid-related weight gain that would occur if UF rates were capped at 13 mL/h/kg without concurrent TT extension or IDWG reduction.

“Implementation of a maximum UF rate threshold without adequate attention to extracellular volume status may lead to fluid-related weight gain.”

Flythe J et al., *BMC Nephrol.* 2017 Jun 2;18(1):185
SUMMARY

"CONTROVERSIS CONFERENCE"... 1st CONTROVERSY MAY BE BLOOD PRESSURE: NOT NECESSARILY HIGHER IN FLUID OVERLOADED PATIENTS

TECHNOLOGIES

(1) FOR VOLUME [DRY WEIGHT] ASSESSMENT
(2) FOR VOLUME MANAGEMENT
(3) FOR STRATEGIC DIALYSIS PLANING

ASSOCIATIONS OF (1) (2) (3) WITH OUTCOMES, PROSPECTIVE MORTALITY BENEFIT UNCLEAR

- Pedal Edema
- Chest X-ray
- Inferior Vena Cava Diameter
- Biochemical Markers
- Lung Comets
- (Diagnostic) Relative Blood Volume Monitoring
- Dual-energy X-ray absorptiometry (=DXA)

- Magnetic Resonance Imaging (MRI)
- Echocardiography
- Pulmonary Artery Pressure
- Pulse Pressure
- Stroke Volume Variation
- Leg Raising Test
- Blood Pressure Measurement
- Bioimpedance (spectroscopy)

- Hemofiltration/Hemodiafiltration
- Cooling
- Sodium Profiling
- Relative Blood Volume-Controlled Feedback of the Ultrafiltration Rate
- Absolute Blood Volume
- Isolated Ultrafiltration

- Session Length
- UF Rate
- Target Weight Achievement

Differentiating between IDWG and Chronic Fluid Overload through [1] objective TW Assessment

TIME FOR...

Turning the Tide: Improving Fluid Management in Dialysis through Technology