Do advances in hemodialysis technology (e.g. the use of biofeedback, blood volume and clearance monitoring) offer better outcomes?

Pro: Antonio Santoro M.D.
Dialysis related complications in Conventional HD

- **Hypertension**
  - Mittal SK, Clin Nephrol, 1999, 51 (2), 77-82
  - Chazot C et al, ND & T, 1995, 10, 831-837

- **Hypotension**
  - Agarwal et al, AJKD, 2008, 51, (2), 242-254

- **Vascular access failure**

- **Cardiac arrhythmias**
  - Narula AS, Ren Fail. 2000
  - Abe S Am Heart J. 1996

- **Micro.macro inflammation**

- **Hospitalization**
  - O’Brien T, AJKD, 2008, 51 (1), S1, S137-154
Intra-dialytic Hypotension may....

- Interfere with the delivery of adequate dialysis
- Induce or aggravate hypoperfusion in different districts:
  - cerebral
  - mesenteric
  - cardiovascular

- Influence the patient outcome
Hemodynamic instability and outcome

The effect of frequent or occasional dialysis-associated hypotension on survival of patients on maintenance hemodialysis

Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients

*P < 0.05, ***P < 0.001 Fatalities vs. survivors

Survival Distribution Function

Fig. 1. Kaplan-Meier survival curves of patients with frequent, occasional and no IDH.

Tisler A, NDT 2003

Hemodynamic stability during HD has to be considered a dialysis ADEQUACY PARAMETER

Shoji T, Kidney Int 2004
Hemodialysis-induced myocardial stunning

PET, for myocardial perfusion assessment

Mc Intyre, CJASN 2008
Hemodialysis-induced myocardial stunning

HEMODIALYSIS

↓ Myocardial blood flow

Myocardial ischemia

Regional wall motion abnormalities

Myocardial dysfunction
Towards a more physiological dialysis

Daily frequency

Long duration

The advantages and challenges of increasing the duration and frequency of maintenance dialysis sessions

Charles Chazot* and Guillaume Jean

doi: 10.1093/ndt/gfn080
Advance Access publication 4 December 2008

Intensifying dialysis: how far should we go and at what cost?

Lieven Annemans

Department of Public Health, Ghent University, Belgium
Incremental cost and incremental life expectancy relative to current practice under baseline assumptions.

The cost-effectiveness ratio increases with the frequency of hemodialysis. More frequent in-center hemodialysis strategies could become cost-neutral if the cost per hemodialysis session could be reduced by 32 to 43%.

Lee CP. et al. JASN 2008;19:1972
Towards a more physiological dialysis

Alternatively or combined with:

*high technology*

- Control of dialysate chemical and physical properties (temperature)
- Control of dialysis efficiency
- Monitoring and control (in open or closed loop) of the hemodynamic patient variables: SAP, TPVR, BV, HR, CO
- Tailoring of ultrafiltration and conductivity by means of feedback control systems
DIALYSIS-RELATED CARDIOVASCULAR INSTABILITY

NON AUTONOMIC CAUSES
- BV volume depletion
- Myocardial insufficiency
- Venodilation
- Stroke vol
- Exessive UFR
- TBW/dry weight < 50%
- Negative Na balance
- Maldistribution of BV

AUTONOMIC CAUSES
- Bezold - Jarish
- Baroreceptor deafferantation
- Sympathetic disfunction

Vaso regulatory impairment
- Decrease in PVR
CONTINUOUS METHODS FOR MEASURING RELATIVE BLOOD VOLUME

Mass conservation principle: blood substances confined to the vascular space change proportionally as a result of changes of the plasma volume.
Relative BV changes

\[ \frac{d \text{BV}}{dt} = - [F_{A(t)} + UF] + R_{V(t)} \]

- Decreasing tissue hydration
- Increasing vasoconstriction

Plasma Volume Change rate = Vascular refilling rate - Ultrafiltration rate
Ultrafiltration rate L/h

Blood volume change, %

\[ y = -9.323x - 6.824 \]

\[ r = -0.33; p = 0.007 \]

\[ n = 102 \]

Mancini et al. IJAO, 1996
### Hematocrit threshold determined by the Crit-Line Instrument When Intradialytic Morbid Events Occurred

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>No. Of IME*</th>
<th>Hematocrit Threshold (mean ±SD)</th>
<th>Mean H change before IME from start of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>40 ± 1.6</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>38 ± 1.3</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>31 ± 2.7</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>46 ± 1.9</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>44 ± 0.5</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>38 ± 2.2</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>44 ± 0.5</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>40 ± 1.2</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>38 ± 0.4</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>49 ± 0.9</td>
<td>11</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
<td>36 ± 0.5</td>
<td>6</td>
</tr>
<tr>
<td>12</td>
<td>7</td>
<td>49 ± 2.2</td>
<td>9</td>
</tr>
</tbody>
</table>

* Total number of IME occurring during the six study sessions for each patient

Steuer R. et al, ASAIO J, 1994
An individual RBV limit exists for nearly all patients and this threshold may mark the individual window of haemodynamic instabilities.
MECHANISMS WHICH CAN AFFECT PLASMA REFILLING DURING DIALYSIS

1. Impairment of peripheral vasoconstriction during volume removal
   - Acetate
   - Release of cytokines (IL1-TNF-IL6)
   - Autonomic neuropathy
   - Thermal stress

2. Increase in hydrostatic capillary pressure
   - Compromised cardiac function
   - Peripheral pooling of blood volume

3. Depletion of interstitial volume
   - Low dialysate sodium concentration
   - High transcellular urea gradient
   - Dry body weight error or high UF

4. Oncotic pressure changes
   - Hypoalbuminemia
   - Alteration in interstitial fluid drainage and lymph flow
Blood volume changes in normo-, over- and under-hydrated patients

In under-hydrated pts. the ratio between BV% changes and ultrafiltration is very high, on the contrary in over-hydrated pts. the same ratio is very low.
The monitoring of RBV trends *alone* may be misleading and confusing.
Intradialytic Blood Volume Monitoring in Ambulatory Hemodialysis Patients: A Randomized Trial


443 HD patients randomized to 6 months to Crit-line conventional monitoring (227) or conventional monitoring (216)
Results

- More non-access-related hospitalizations were seen in the BVM compared with conventional groups (120 vs 81 episodes).

- The unadjusted and adjusted risk ratios for non-access-related hospitalization were 1.49 and 1.61, respectively.

- The adjusted risk ratios for cardiovascular admissions was 1.85.

- The mortality at 6 months was greater in the BVM than the conventional monitoring (8.7% vs 3.3%).
Limitations to the study

- The study population was not limited to those with clinical issues of volume management and hemodynamic instability.

Changes in the profiles without any correlations with UF and body weight of the patients were intended to support modifications in the target post-dialysis weight and/or antihypertensive medications and hospitalization rate, which may exacerbate the differences between the two groups.

- Cause of hospitalization was not centrally adjudicated.

- The study period only 6 months, a longer horizon might have different findings.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Intervention</th>
<th>Primary end point</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-IDH-prone Population Reddan (JASN 2005)</td>
<td>RCT</td>
<td>Crit-line (conventional monitoring)</td>
<td>Morbidity</td>
<td>Increased hospitalization in BVM group, Adjusted RR 1.61 (95% CI 1.15–2.25)</td>
</tr>
<tr>
<td>Gabrielli (JN 2009)</td>
<td>Cross-over RCT</td>
<td>Fresenius 4008HD (conventional monitoring)</td>
<td>Intra-dialytic morbidity</td>
<td>Reduction in IDH in BVM group (24% vs 32%, $P = 0.04$)</td>
</tr>
</tbody>
</table>
RBV behaviour in normohydrated pt.

RBV behaviour in overhydrated pt.
Clinical significance of Monitoring the Blood Volume variations

Assessment of plasma refilling rate

“The use of dynamic test, based on ultrafiltration stops, may be useful for optimising the patient’s dry-weight and to evaluate the individual capillary filtration coefficient.”

Linear Decay of Relative Blood Volume During Ultrafiltration Predicts Hemodynamic Instability

Sandip Mitra, MD, Paul Chamney, PhD, Roger Greenwood, MD, and Ken Farrington, MD

American Journal of Kidney Diseases, Vol 40, No 3 (September), 2002: pp 556-565

Fig 1. A typical RBV profile obtained in response to a UF pulse showing decay, subsequent refill phase, and measured parameters. Values for ΔRBV in percentage, and for IRR, in percentage per minute. Abbreviation: ΔRBVref, the magnitude of RBV change during the refill phase, in percentage.
### Chi-Square Analysis Comparing UF and Refill Characteristics Between Hypotensive and Normotensive UF Pulses

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hypotensive UF Pulses (n=30)</th>
<th>Normotensive UF Pulses (n=60)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBV at UF pulse initiation (%)</td>
<td>90.5±4.2</td>
<td>94.6±3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>∆RBV$_{UF}$ (%)</td>
<td>7.4±1.8</td>
<td>6.9±1.5</td>
<td>NS</td>
</tr>
<tr>
<td>UFV$_S$(mL)</td>
<td>457±123</td>
<td>457±123</td>
<td>NS</td>
</tr>
<tr>
<td>∆RBV$_{UF}$/UFV$_S$(%/mL)</td>
<td>0.017±0.005</td>
<td>0.016±0.004</td>
<td>NS</td>
</tr>
<tr>
<td>UF decay amplitude (b)</td>
<td>71.2±12.9</td>
<td>79.4±13.9</td>
<td>0.007</td>
</tr>
<tr>
<td>τ$_{UF}$</td>
<td>21.6±8.5</td>
<td>12.8±2.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Linear divergence (%.s)</td>
<td>155±285</td>
<td>662±405</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IRR (%/min)</td>
<td>0.86±0.45</td>
<td>0.76±0.35</td>
<td>NS</td>
</tr>
<tr>
<td>Refill phase amplitude</td>
<td>3.4±1.1</td>
<td>4.8±2.4</td>
<td>0.001</td>
</tr>
<tr>
<td>τ$_{ref}$</td>
<td>0.25±0.69</td>
<td>0.14±0.10</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Mitra S; Am J Kidney Dis 2002;40:556-565*
## Covariates related to symptomatic hypotension

### multivariate logistic regression

<table>
<thead>
<tr>
<th></th>
<th>p</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>C vs A</strong></td>
<td>NS</td>
<td>1.25</td>
<td>0.54-2.89</td>
</tr>
<tr>
<td><strong>B vs A</strong></td>
<td>&lt;0.001</td>
<td>7.26</td>
<td>3.07-17.13</td>
</tr>
<tr>
<td><strong>Baseline plasma-dialysate Na(^+) gradient (for each 1 mEq/L increase)</strong></td>
<td>&lt;0.001</td>
<td>1.13</td>
<td>1.06-1.22</td>
</tr>
<tr>
<td><strong>Δ BV from 20 to 40 min of dialysis (for each 1% decrease)</strong></td>
<td>0.030</td>
<td>1.23</td>
<td>1.02-1.48</td>
</tr>
<tr>
<td><strong>Irregularity of BV over time (yes/no)</strong></td>
<td>0.001</td>
<td>3.13</td>
<td>1.65-5.96</td>
</tr>
<tr>
<td><strong>HR decrease from the start to the 20(^{th}) min of dialysis (for each 1 beat/min decrease)</strong></td>
<td>0.017</td>
<td>0.95</td>
<td>0.91-0.99</td>
</tr>
</tbody>
</table>

Andrulli S, Am J Kidney Dis 2002
Blood volume tracking
SYSTEM

Patient → BV Monitor → DC Monitor → BWL Monitor → MIMO Controller → Dialysis Machine

Δ%RBV → DC → WLR → Errors

Δ%BV Target → DC_eq target → BWL Target

Blood Volume Tracking

Santoro A. AJKD1998
The first experiences with the biofeedback control of Blood Volume

### Summary of randomized BVM and BVT trials, characterized by study population

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Intervention</th>
<th>Primary end point</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional BV monitoring</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-IDH-prone Population Reddan (JASN 2005)</td>
<td>RCT</td>
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<td>Gabrielli (JN 2009)</td>
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<td>Intra-dialytic morbidity</td>
<td>Reduction in IDH in BVM group (24% vs 32%, P = 0.04)</td>
</tr>
<tr>
<td>Santoro (KI 2002)</td>
<td>Cross-over RCT</td>
<td>BVT (conventional HD)</td>
<td>IDH reduction</td>
<td>30% reduction in IDH, (P = 0.004) sessions in BVT Group</td>
</tr>
<tr>
<td>Ronco (KI 2000)</td>
<td>Cross-over RCT</td>
<td>BVT (conventional HD)</td>
<td>IDH reduction</td>
<td>Less IDH in BVT group (24 vs 59 HDx sessions, $P \leq 0.001$)</td>
</tr>
<tr>
<td>Nersallah (ASAIO J 2008)</td>
<td>RCT</td>
<td>Hemo-biofeedback systems (conventional monitoring)</td>
<td>Change in ECV at 6 months</td>
<td>Lower IDH in HBS group (0.13 vs 0.31) $P = 0.04$</td>
</tr>
</tbody>
</table>
A multicenter cross-over RCT

A = conventional HD
B = Blood Volume tracking HD

Randomisation

Sequence 1

Sequence 2

A

B

A

B

A

B

Run In

Experimental phase

0 2 6 10 14 18

time (weeks)

36

33

3 protocol violators

1 drop out

32

patients

Santoro A. et al., Kidney Int 2002
30% reduction in IDH during BV tracking HD

### Dialysis efficiency

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Biofeedback</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Pool Kt/V</td>
<td>1.34 ± 0.08</td>
<td>1.26 ± 0.06</td>
<td>p&lt; 0.005</td>
</tr>
<tr>
<td>Equilibrated Kt/V</td>
<td>1.03 ± 0.08</td>
<td>1.12 ± 0.05</td>
<td>p&lt; 0.001</td>
</tr>
<tr>
<td>Urea Rebound %</td>
<td>14.2 ± 2.7</td>
<td>6.4 ± 2.3</td>
<td>p&lt; 0.001</td>
</tr>
<tr>
<td>Urea removal (grams)</td>
<td>30.4 ± 4.1</td>
<td>35.4 ± 3.7</td>
<td>p&lt; 0.005</td>
</tr>
<tr>
<td>Solute Removal Index</td>
<td>1.77 ± 0.15</td>
<td>2.01 ± 0.23</td>
<td>p&lt; 0.005</td>
</tr>
</tbody>
</table>

Bland-Altman test (N=144 dialysis sessions)

Impact of biofeedback-induced cardiovascular stability on hemodialysis tolerance and efficiency
Intradialytic hypotension

The number of dialysis complicated by hypotensions over the total number of assessed dialysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>HBS (Yes)</th>
<th>HBS (No)</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>1994 Santoro (1)</td>
<td>1</td>
<td>30</td>
<td>13</td>
<td>30</td>
</tr>
<tr>
<td>1998 Santoro (2)</td>
<td>25</td>
<td>96</td>
<td>68</td>
<td>192</td>
</tr>
<tr>
<td>2000 Ronco</td>
<td>24</td>
<td>72</td>
<td>59</td>
<td>72</td>
</tr>
<tr>
<td>2001 Basile (3)</td>
<td>26</td>
<td>171</td>
<td>45</td>
<td>171</td>
</tr>
<tr>
<td>2002 Santoro</td>
<td>180</td>
<td>766</td>
<td>256</td>
<td>766</td>
</tr>
<tr>
<td>2002 Wolkotte</td>
<td>10</td>
<td>158</td>
<td>28</td>
<td>157</td>
</tr>
<tr>
<td>2003 McIntyre</td>
<td>2</td>
<td>133</td>
<td>13</td>
<td>133</td>
</tr>
<tr>
<td>2006 Moret (4)</td>
<td>9</td>
<td>110</td>
<td>18</td>
<td>110</td>
</tr>
<tr>
<td>2007 Deziel (5)</td>
<td>56</td>
<td>204</td>
<td>63</td>
<td>228</td>
</tr>
<tr>
<td>2008 Winkler (6)</td>
<td>1</td>
<td>648</td>
<td>9</td>
<td>108</td>
</tr>
</tbody>
</table>

Total (95% CI) 2388 1967 100.0% 0.35 [0.21, 0.56]

Total events 334 572

Heterogeneity: Tau² = 0.38; Chi² = 47.17, df = 9 (P < 0.00001); I² = 81%
Test for overall effect: Z = 4.38 (P < 0.0001)

(1) Data pooled over A1, A2 study phases
(2) Data pooled over A1, A2 study phases
(3) Data referred to the short-term study phase
(4) Data referred to the conventional vs HBS phases
(5) Data referred to 4 weeks recording (2 weeks at the beginning and 2 weeks at the end)
(6) Data referred to the short-term study phase

Santoro A. submitted
EBPG guideline on hemodynamic instability

Guideline 3.1.2a Individualized, automatic BV control should be considered as a second-line option in patients with refractory IDH (Evidence level II).

Rationale

With blood volume controlled treatments, ultrafiltration rate and/or dialysate conductivity are adjusted according changes in relative blood volume.

[...] Nevertheless, several randomized cross-over studies have shown a reduction in IDH and intra-dialysis symptomatology with the use of automatic blood volume feedback [1,2,4-6]. Moreover, one study showed an increase in dialysis efficacy with the use of this approach, due to a reduction in intra-dialytic interventions [1].

[...] No adverse effects on sodium balance have yet been reported [2,7].

[...] Summarizing, various studies have shown a beneficial effect of automatic blood volume controlled feedback in the prevention of IDH episodes.

NDT (2007) 22 [Suppl. 2]: ii22-ii44
Measurement of blood volume during hemodialysis is a useful tool to achieve safety adequate dry weight by enhanced ultrafiltration

Method: N=12
- Single dry weight reduction the mid-week dialysis = -0.5 Kg
- BV reduction recording

Results:
- 58 % of patients were successful (no symptoms)
- 42 % of patients failed (symptoms)

• Prospective, randomized, parallel group study with two arms (standard HD vs BVT)
• Study duration: 4 wk Run-in + 12 weeks
• Enrolled patients = 28 (14 per arm)
• Hypertensive pts (pre-HD and/or post-HD BP >150/90 mmHg) in antihypertensive treatment or with cardiorotoracic ratio >0.5
• No intervention were designed in each arm to reduce the dry body weight but the judgment of the nephrologists according to the overhydration status
Effects of Relative Blood Volume-Controlled Hemodialysis on Blood Pressure and Volume Status in Hypertensive Patients

JUDITH J. DASELAAR,∗+ ROEL M. HUISMAN,∗+ PAUL E. DE JONG,∗ JOHANNES G. M. BURGERHOF,+ AND CASPER F. M. FRANSSEN†

○ Standard-HD
● BVT

Pre-Hemodialysis

On average a reduction of 0.7Kg in the dry weight was observed in the first 3 weeks
Effects of Relative Blood Volume–Controlled Hemodialysis on Blood Pressure and Volume Status in Hypertensive Patients

Judith J. Dasselaar,†† Roel M. Huysman,†† Paul E. de Jong,*,† Johannes G. M. Burgerhof,‡ and Casper F. M. Franssen‡‡

Pre-Hemodialysis

A

ECW/BW (L/kg)

0

0.1

0.2

0.3

0.4

Time (weeks)

0

12

B

ECW/BW (L/kg)

0

0.1

0.2

0.3

0.4

Time (weeks)

0

12

Weeks

ECW/TBW

0,22

0,24

0,26

0,28

0

12

p<0,01

BVT

Standard HD
Conclusions

- RBV monitoring has to be adjusted for UF rate and weight in determining BV and hydration status.

- BV controlled HD (Hemo-biofeedback systems) proved useful to improve the hemodynamic stability and the overall tolerance to the HD treatment in DH-prone population.

- Frail, critical, co-morbid patients are the target patient population for BV controlled HD.

- EBPG consider automatic BV control in the strategies to prevent hemodynamic instability.

- Furthermore BV controlled HD has been shown to be useful in the assessment of IBW in hypertensive pts. with latent over-hydration.
Factors influencing KT/V

K  filter type, priming, Qb, clotting, ...
T  by-passes, blood pump stops
V  dry weight, hydration status
Problems with conventional adequacy assessment

- V- based dose measure may result in underdialysis of women/children/smaller patients
- May fail to detect marked underdialysis if postBUN drawn incorrectly
- Expense of monthly postBUN blood drawn
- Once-a-month measurement may not reflect monthly treatment (shortened, missed treatments)
  - Large month-to-month variability
Current on-line adequacy methods

- Estimation of on-line dialyzer clearance using sodium conductivity

- Measuring or estimating the change in spent dialysate urea during the treatment
Advantages of automated monitoring of K or urea removal

- Elimination of pre- and post-dialysis blood urea nitrogen measurement
- Ensuring that the patient receives the prescribed dose of dialysis each time
- More accurate delivery of a dialysis prescription to new patients
- Detection of access recirculation
- Performing quality assurance of reprocessed dialyzers
The aims of on-line monitoring

- Keeping under continuous control physiological, biochemical and haemodynamic parameters.
- Preventing critical clinical situations
- Modifying, in open-loop or with automatic feedback (closed loop) the dialysis actuators
Limiting factors in intradialytic online monitoring

- Extra costs
- Plentifully signals and poor knowledge
- Polyedral interpretation
- Larger validation studies in different groups of patients may be needed so as to evaluated actual outcome effect