Fluid management in Peritoneal Dialysis patients

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Objective and outline

1. Assessment of volume status

2. Bioimpedance study in PD patients

3. Cardiovascular and non-cardiovascular consequences of fluid overload

4. Bioimepedance-guided fluid management
Trends in the prevalence of patients on peritoneal dialysis in Asia between 1999 and 2013

- PD is a cost-effective, home-based modality of RRT
- Utilization of PD is increasing in some countries, including China, the USA and Thailand

Cardiovascular disease is common in ESRD patients

USRDS 2018
## Non-traditional risk factors of CVD

### Table 1. Manifestations of cardiovascular disease in chronic kidney disease and associated putative risk factors

<table>
<thead>
<tr>
<th>Traditional risk factors</th>
<th>Nontraditional risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>Albuminuria</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Reduced glomerular filtration rate</td>
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<tr>
<td>Valvular disease</td>
<td>Anemia</td>
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<tr>
<td>Dyslipidemia</td>
<td>Inflammation</td>
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<tr>
<td>Smoking</td>
<td>Arteriosclerosis</td>
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<tr>
<td>Diabetes</td>
<td>Extracellular fluid volume overload</td>
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<td></td>
<td>Abnormal calcium/phosphate metabolism</td>
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</tbody>
</table>

Assessment of volume status

Challenges and pitfalls
Fluid status assessment is not easy

- **Physical examination**
  - Blood pressure
  - BW, BMI
  - Peripheral oedema, raised JVP, lung crepitation

- **Biomarkers**
  - BNP, pro-BNP

- **Lung ultrasonography**

- **Body fluid compartment by solute or isotope dilution**
  - TBW, ECW, ICW
  - Research purposes only
Blood pressure and volume of overhydration in PD

SBP were correlated with OH (r = 0.58) in 122 PD patients

12.3% overhydrated patients were normotensive

BMI in body composition assessment

- **Pitfall**: BMI does not distinguish between fat, muscle mass and excessive fluid

- 49 stable outpatient patients (CrCl<60ml/min) vs 298 controls
- BMI and BW similar
- Absence of edema/sign of malnutrition

Discordance between ΔBW and Δbody composition

- 60 incident PD patients
- BW continued to increase during the 12 months, but visceral fat mass increased during the first 6 months then decreased

What about new investigations?

• Biomarker
  • ANP, BNP, NT-proBNP
  • Atrial stretch, ventricular filling pressure
  • **Problem**: lack specificity

• Lung ultrasonography
  • Detect extravascular lung water (EVLW): fluid in lung interstitium
  • **Problem**: operator-dependent

Bioimpedance study

• Principle
  • Flow of small amplitude, alternating electrical current
  • Determine body composition by fitting impedance data into mathematical model

• Variants
  • Bioelectrical impedance analysis (BIA) vs bioimpedance spectroscopy (BIS)
  • Single vs multifrequency
  • Segmental vs whole body

• Validated in general population and dialysis patients

Mossi et al. Physiol Meas 2006; 27:921–933
Body Composition Monitor (BCM)

- Multi-frequency whole body bioimpedance spectroscopy (BIS)
- What does it do?
  - Measures at 50 frequencies over a range from 5 to 1000kHz
- What results does it generate?
  - ECW, ICW, TBW

[Diagram showing body composition with ECW, ICF, ECF, and cells at different frequencies]

Low frequency

High frequency
Three-compartment model

• adipose tissue mass (ATM) + lean tissue mass (LTM) + volume of overhydration (OH)

• Hydration parameters:
  OH (liter) (eg, >1.1L)
  OH/ECW (%) (eg, >7%)

• Nutritional parameters:
  ATM (kg), LTM (kg)
Body Composition Monitor (BCM)

- **Strength:**
  - Objective
  - Convenient
  - Non-invasive
  - Highly reproducible
  - Point-of-care service

- **Limitations**
  - Amputation
  - Metallic prostheses, pacemakers
  - Extreme BMI

Bioimpedance study in PD patients

How common is fluid overload?
Who is at risk?
Overhydration is common at the beginning of dialysis

- 56.5% had OH > 1.1L
- > 30% of incident PD patients, who are considered euolemic or dehydrated by clinical assessment, have fluid overload by BCM

EuroBCM Study: fluid overload in prevalent PD patients

- 639 prevalent PD patients from 28 centres in 6 European countries

- Fluid overload (relative tissue hydration [OH/ECW] >7%): 53.4%
- Severe fluid overload (relative tissue hydration ≥15%): 25.2%

- Higher relative tissue hydration was independently associated with:
  - older age
  - Male gender
  - lower serum albumin
  - lower BMI
  - Diabetes
  - but not...
  - Transporter status
  - Residual urine output

Overhydration is common in asymptomatic patients

- 88/122 patients (72.1%) had overhydration $\geq 1$ L
- 25/122 patients (20.5%) had overhydration $\geq 5$ L

Risk factors for fluid overload

Most common associations:
- Older age
- Presence of DM
- Higher SBP
- Low albumin
- Probably no strong relation with RRF or PD modality

Ng JK, Li PK. Fluid management and bioimpedance in peritoneal dialysis. Curr Opin Nephrol Hypertens. 2019
Does RRF eliminate the risk of fluid overload?

- There was no significant difference in diuretics use, UF volume and residual urine output between overhydrated and euveleemic patients.

- Reason?
  - Volume status = intake – (ultrafiltration + diuresis)
  - Dietary compliance matters!

Does hypervolemia help to preserve RRF?

Myth: PD patients should be ‘slightly’ hypervolemic to avoid loss of RRF
(a) lower hydration tertile, (b) middle hydration tertile, (c) upper tertile.

- There was no significant correlation between change in hydration status and change in RRF in any of the three tertiles

Clinical consequences of bioimpedance-defined fluid overload

<table>
<thead>
<tr>
<th>Study population</th>
<th>O’Lone et al. [34]</th>
<th>Guo et al. [35]</th>
<th>Ng et al. [36*]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalent and incident CAPD + APD (n = 529)</td>
<td>Prevalent CAPD (n = 307)</td>
<td>Incident CAPD + APD (n = 311)</td>
<td></td>
</tr>
<tr>
<td>Duration of follow-up (median)</td>
<td>27 months</td>
<td>38.4 months</td>
<td>27.3 months</td>
</tr>
<tr>
<td>All-cause mortality (hydration parameters were continuous variables in [34,36*] and categorical variables in [35], respectively)</td>
<td>OH (per litre): HR 1.10 (95% CI 1.01–1.20) OH/ECW (per 1%): HR 1.03 (95% CI 1.01–1.05) ECW/TBW (per 10%): HR 1.21 (95% CI 0.95–1.54)</td>
<td>FO defined by ECW/TBW ≥0.40: HR 12.98 (95% CI 1.06–168.2)</td>
<td>OH (per litre): HR 1.10 (95% CI 1.03–1.18) OH/ECW (per 1%): 1.02 (95% CI 1.00–1.05) ECW/TBW (per 1%): 1.08 (95% CI 1.01–1.15) E/I ratio (per 0.1): 1.24 (95% CI 1.05–1.40)</td>
</tr>
<tr>
<td>Technique failure</td>
<td>Not studied</td>
<td>FO defined by ECW/TBW ≥0.40: HR 13.56 (95% CI 2.53–78.69)</td>
<td>NS</td>
</tr>
<tr>
<td>CV event-free survival, excluding CHF</td>
<td>Not studied</td>
<td>Not studied</td>
<td>OH (per litre): HR 1.07 (95% CI 1.01–1.15) OH/ECW (per 1%): 1.02 (95% CI 1.00–1.04) ECW/TBW (per 1%): 1.07 (95% CI 1.01–1.13) E/I ratio (per 0.1): 1.19 (95% CI 1.05–1.36)</td>
</tr>
</tbody>
</table>

APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular, ECW extracellular water; E/I ratio, ratio of extracellular water to intracellular water; FO, fluid overload; HR, hazard ratio; NS, nonsignificant; OH, overhydration volume; TBW, total body water.

Ng JK, Li PK. Fluid management and bioimpedance in peritoneal dialysis. Curr Opin Nephrol Hypertens. 2019
BIS-defined FO and patient survival

• 529 prevalent + incident PD patients

• Severely overhydrated patients (highest 30% in the cohort) had approximately 2-fold increase in mortality

**Predictor of survival in asymptomatic incident PD patients (competing risk model)**

Each 1L in OH = 9.6% in mortality

<table>
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<tr>
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<th>Patient survival</th>
<th>Technique survival</th>
<th>CV event-free survival, including CHF</th>
<th>CV event-free survival, excluding CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACSHR</td>
<td>P value</td>
<td>ACSHR</td>
<td>P value</td>
</tr>
<tr>
<td>OH (per L)</td>
<td>1.096</td>
<td>p = 0.009</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CCI (per unit)</td>
<td>1.138</td>
<td>p = 0.033</td>
<td>1.191</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>albumin (per g/L)</td>
<td>0.952</td>
<td>p = 0.051</td>
<td>0.958</td>
<td>p = 0.055</td>
</tr>
<tr>
<td>SBP (per 10 mmHg)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age (per 10 year)</td>
<td>1.446</td>
<td>p = 0.015</td>
<td>-</td>
<td>-</td>
</tr>
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</table>

Abbreviations: ACSHR, adjusted cause-specific hazard ratio; CHF, congestive heart failure; CV, cardiovascular; OH, volume of overhydration; CCI, Charlson’s Comorbidity Index; SBP, systolic blood pressure.

*Similar result when OH/ECW or ECW/TBW was used*

Ng JK... Li PK, et al. Asymptomatic fluid overload predicts survival and cardiovascular event in incident Chinese peritoneal dialysis patients. PLoS One 2018
Relations between malnutrition-inflammation-atherosclerosis and volume status

95 prevalent PD patients in an university dialysis center

<table>
<thead>
<tr>
<th>m-BIA parameters</th>
<th>Volume parameters</th>
<th>Inflammation</th>
<th>Atherosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LAD/h</td>
<td>SBP</td>
<td>CRP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CTI</td>
<td></td>
</tr>
<tr>
<td>TBW/h</td>
<td>0.327&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.366&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.196</td>
</tr>
<tr>
<td>ICW/h</td>
<td>0.250&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.377&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.134</td>
</tr>
<tr>
<td>ECW/h</td>
<td>0.439&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.332&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.287&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>DLM/h</td>
<td>-0.172</td>
<td>0.137</td>
<td>-0.029</td>
</tr>
<tr>
<td>PA°</td>
<td>-0.165</td>
<td>0.093</td>
<td>-0.330&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Hydration status was significantly correlated with echocardiographic parameters, C-reactive protein (CRP) and carotid artery intima-media thickness (CA-IMT)

Chronic fluid overload is worse

- 284 prevalent PD patients
- Prospective observational study
- BCM at baseline and 12 months later
- 26.7% (n=76) had FO at baseline; 68.4% (n=56) of them remained in chronic FO

Kim JK, et al. Repeated Bioimpedance Measurements Predict Prognosis of Peritoneal Dialysis Patients. AJN 2018
‘Non-CV’ impacts of fluid overload
Malnutrition-inflammation complex and fluid overload

• Fluid overload is...
  • commonly associated with hypoalbuminemia
  • More pronounced in PD patients (peritoneal protein loss)
  • associated with increased inflammatory burden

Li PKT, Ng JK, McIntyre CM. Semin Nephrol 2017;37(1):54-65
The ‘leaky’ gut and consequence of bacterial fragment translocation in CKD patients

In CKD patients, gut microbiota is altered
- Increased in expression of urease and uremic toxic-forming enzymes
- Disrupted gut barrier function
- Translocation of bacteria

Szeto CC, McIntyre CW, Li PKT. J Am Soc Nephrol 2018; 29(6): 1601-1608
Endotoxemia in PD patients

- Bacterial endotoxin is a lipopolysaccharide (LPS) which constitutes the major glycolipid component of the outer membrane of gram-negative bacteria

Endotoxemia in PD patients

- endotoxemia may have a contributory role to the systemic inflammatory state and accelerated atherosclerosis in PD patients

Frailty: geriatric syndrome in renal patients

- Fried criteria (2001)
  - Unintentional weight loss (≥10 lb in 1 year)
  - Slow walking speed (lowest 20% adjusted for height and gender)
  - Weak grip strength (lowest 20% adjusted for BMI and gender)
  - Exhaustion (self-report)
  - Low physical activity (lowest 20% adjusted for gender)

- Frail: ≥ 3
- Pre-frail: 1-2

Frailty + ESRD = bad combination

Frailty

Death
Risk x 2.2–2.4

Hospitalization
Risk x 1.6–1.8

Frailty and hydration status in PD patients

- 193 prevalent PD patients, mean age = 60 +/- 12 years, mean BMI 24.9
- 69% were frail (cumulative deficit model [questionnaire score 0-30])

The association of OH with frailty suggests that hypervolemia was associated with poor physical function.

Fluid management in PD

Role of bioimpedance study
Strategy to maintain euvoolemia

• Dietary restriction of salt and fluid intake
• Maximize diuresis
• Adaptation of dwell time to transporter status
• Judicious use of hypertonic exchanges +/- icodextrin
• Increase the awareness among patient and clinicians
• Prepare for transition from PD to HD

Kim YL, van Biesen W. Fluid overload in peritoneal dialysis patients. Semin Nephrol 2017
The value of longitudinal bioimpedance study on fluid management of peritoneal dialysis patients

- A prospective, randomized, open-label, blinded end-point controlled trial

- 308 PD patients in 4 PD centers (three in UK, one in China)

- Intervention group: clinical assessment + longitudinal Bioimpedance (BI) measures (as vector plots every 3 months)

- Control group: ordinary clinical assessment

- Hypothesis: To investigate whether availability of longitudinal BI measures helped clinicians to maintain stable fluid status over 12 months

The value of longitudinal bioimpedance study on fluid management of peritoneal dialysis patients

• Non-anuric patients: there were no significant changes in body composition over the 12-month study period.

• Anuric patients: hydration status (ECW/TBW) worsened in both intervention and control group.

• Study design was intended to show how BI may be used to detect longitudinal changes in body composition and to adjust for these rather than using it as a tool to drive patients to a specific target hydration status.

• Conclusions: routine use of longitudinal BI vector plots had minimal impact on fluid management.

• Caveat: complex and repeated intervention; different center practice.

COMPASS trial: does BIS guide our direction on fluid management?

- **Design:** Multicenter, prospective, open-label, randomized-controlled trial
- **Study population:** non-anuric (>500ml/day) PD patients
- **Intervention:** 67 BIS group vs 70 control group

**Outcomes:**
- No difference in change of residual GFR (-1.5 ± 2.4 vs -1.3 ± 2.6 mL/min/1.73 m², p = 0.59)
- No difference in majority of body composition parameters (including OH and OH/ECW)
- No difference in echo parameters (including LVEF and LVMi)

Oh KH, et al. Does bioimpedance-guided fluid management provide additional benefit in non-anuric PD patients? Results from COMPASS trial. PDI 2018
Hydration parameters were stable over 12 months

- Routine BIS-guided fluid management did not provide additional benefits in volume status control and RRF preservation

- Caveat:
  - ? selection bias: only include patients with low comorbidity and albumin >33g/L

Take home messages

• Fluid overload in PD patients is common
  • asymptomatic and present in the beginning of dialysis
• Bioimpedance spectroscopy (BIS) is a validated tool which can provide objective and accurate assessment of hydration status in a standardized manner
• Estimation of body composition (adipose tissue, lean tissue, overhydration) by BIS may be more informative than body weight or BMI
• Fluid overload, together with inflammation and malnutrition, represent a cluster of non-traditional risk factors which contribute to the excessive mortality and morbidity
• BIS-defined fluid overload is associated with increase in all-cause mortality, technique failure and CV event