Proto-dialytic cardiac function relates to intra-dialytic morbid events

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**Abstract**

**Background.** Intra-dialytic morbid events (IDME) such as intra-dialytic hypotension (IDH) and muscle cramps frequently complicate haemodialysis (HD). Cardiac dysfunction is highly prevalent in HD patients. We investigated the relationship between proto-dialytic (i.e. early intra-dialytic) cardiac function and IDME in HD patients.

**Methods.** Heart rate, beat-to-beat blood pressure (BP) and cardiac output were continuously measured during the first 30 min of dialysis treatment using the Task Force™ Monitor. Total peripheral resistance index (TPRI) was calculated from cardiac index (CI) and BP. Univariate, multivariate and logistic regression analyses were employed to relate IDME to haemodynamic predictors; Kaplan–Meier method was employed for time-to-event analysis.

**Results.** Fourteen HD patients (age 67 ± 15 years; 7 females) were studied. Dialysis treatment was complicated by IDH and muscle cramps in 4 and 8 out of 30 sessions, respectively. CI was higher in patients without IDME (2.6 ± 0.5 L/min/m²) as compared to those with muscle cramps (2.0 ± 0.3 L/min/m²) or IDH (1.8 ± 0.2 L/min/m²; all P < 0.05).

CI and TPRI at baseline independently predicted IDME in a multivariate regression analysis (odds ratio: 0.043 per unit of CI, 95% confidence interval: 0.003–0.611; odds ratio: 1.124 per unit of TPRI, 95% confidence interval: 1.25–1.01). Patients were stratified by tertiles of CI. IDME occurred in the two lower tertiles, whereas patients in the upper tertile were event free (log-rank test, P < 0.002).

**Conclusions.** Low CI and high TPRI in the first 30 min of HD are associated with an increased risk of IDME.

**Keywords:** cardiac function; haemodialysis; haemodynamic monitoring; hypotension; intra-dialytic morbid events

**Introduction**

Intra-dialytic hypotension (IDH) and muscle cramps (collectively termed intra-dialytic morbid events; IDME) are the most common complications during maintenance
haemodialysis (MHD), occurring in 20–30% and 33–86% of dialyses, respectively [1–4]. The unpleasant clinical symptoms associated with IDME often result in early termination of dialysis sessions, consequently leading to inadequate dialysis dose, fluid removal and impaired rehabilitation. Moreover, IDME consume a significant amount of dialysis staff time and resources.

IDH has been given a role in myocardial and cerebral ischaemia, long-term fistula atrophy, frontal lobe atrophy and non-occlusive mesenteric ischaemia [5–8]. Although repeated episodes of IDH have been reported to be associated with increased mortality in MHD patients, it remains elusive whether IDH plays a causative role in adverse outcome or is merely a marker of comorbid conditions [9]. Nonetheless, the association between IDH and non-compliance/under-dialysis or inadequate vascular access has been shown to be independently related to increased mortality [10,11].

Various studies have sought to identify risk factors for IDH, such as age, diastolic dysfunction, autonomic neuropathy, low albumin, renal diagnosis other than glomerulonephritis, hyperphosphataemia and the use of nitrates, yet there is no reliable variable available which allows us to protect the occurrence of IDH during a dialysis session [9,12–17]. Estimation of ‘dry weight’ is an area of significant research and clinical interest, but to date no method has been proven accurate and easily applicable. Vena cavaography has been shown to reduce the incidence of IDH and improve quality of life; however, this technique is highly operator dependent and needs to be performed by a specially trained technician [18–20]. In addition, many underlying causes for the development of IDH have been described, such as impaired baroreceptor sensitivity, cardiac dysfunction or a reduction of sympathetic activity, yet the pathophysiology behind it is not fully understood [21–26].

In recent years, the Task Force Monitor (TFM; CNSystems, Austria) has gained increased application in continuous beat-to-beat assessment of cardiovascular variables, such as stroke volume (SV) and cardiac index (CI) by impedance cardiography (ICG). Furthermore, the TFM measures beat-to-beat systolic, diastolic and mean arterial blood pressure (MABP) by the vascular unloading technique [27].

Previous studies have validated cardiac output measurements by thoracic bioimpedance against reference methods (e.g. right-sided catheter) [28,29]. The TFM has been frequently used in cardiology and intensive care settings [30–32]. Recently, it has also been validated against an established indicator dilution technique as a practical non-invasive device for the continuous beat-to-beat monitoring of cardiac output in MHD patients [33]. This makes ICG a promising technique to help shed light on the underlying pathophysiological mechanisms of IDH and to guide physicians in their decision-making process when prescribing dialysis therapy.

The present study was undertaken to early recognize and characterize patients at risk for the development of IDME. Our specific aim was to investigate in a cohort of MHD patients under clinical ‘real-life’ conditions, whether haemodynamic parameters, measured by TFM, within the first 30 min of dialysis therapy (i.e. the proto-dialytic period) are related to subsequent IDME, in particular IDH and muscle cramps.

Materials and methods

Patients on standard three times weekly MHD with an arterio-venous fistula as vascular access were enrolled after giving their written informed consent. The study was approved by the Institutional Review Board of the Krankenhaus der Barmherzigen Brüder, Graz, Austria.

A total of 30 dialysis sessions were performed in 14 patients receiving high-flux HD. Patients were studied on at least two occasions, both after the weekend and midweek. The dialysate temperature was kept constant at 36.5°C. Patients did not consume food during treatment and were advised not to take antihypertensive drugs before or during dialysis. No patient had clinical signs of cardiac insufficiency and overhydration. Post-dialysis target weight (‘dry weight’) was determined clinically on a weekly basis and by employing echocardiography and chest X-ray studies as needed, but not less than twice a year. The dialysate used was bicarbonate-based with a sodium concentration of 138 mEq/L. Fluid removal was held constant throughout each dialysis session using a dialysis machine equipped with a volumetric ultrafiltration control system (Gambro AK 400). Pre-and post-dialysis body weights were measured. Intra-dialytic muscle cramps and episodes of IDH (i.e. IDME) requiring staff intervention were recorded. IDH was defined, according to the European Dialysis and Transplant Association and K/DOQI guidelines, as a decrease in systolic BP >20 mm Hg associated with clinical events and need for nursing interventions [34].

TFM measurements

ICG measures intra-thoracic fluid shifts during a cardiac cycle. TFM electrodes were attached to the patient as described elsewhere [35]. SV is calculated by the equation of Sramek et al.

\[
SV = V_\text{th} \times L\text{VET} \times \frac{\left(\frac{dZ}{dt}\right)_{\text{max}}}{Z_0}
\]

with LVET being the left ventricular ejection time (seconds), \(Z_0\) the base impedance (kilo Ohms) and \(t\) the time (seconds). \(V_\text{th}\), the electrically participating thoracic volume is calculated as

\[
V_\text{th} = (0.17H)^3 / 4.2
\]

where \(H\) is the body height.

Cardiac output (CO) is calculated as the product of SV and heart rate (HR)

\[
CO = SV \times HR.
\]

The crucial element of CO measurements with ICG is to obtain a good estimate for \(V_\text{th}\). Hence, Sramek et al. estimate \(V_\text{th}\) by modelling the thorax as a truncated cone or frustum, respectively [35]. Underweight people are expected to have a more cylindrical thorax shape whereas obese will have a more frustum-shaped thorax. In a new aspect of estimating \(V_\text{th}\), the influence of body composition (by body mass index; BMI) as well as of the base impedance \(Z_0\) is considered

\[
V_\text{th} = C_1 \times H^n \times \frac{\text{BMI}^m}{Z_0}
\]

where the scaling factor \(C_1\) and the powers \(n\) and \(m\) are subject to proprietary non-disclosure [35].

Cardiac index (CI) is calculated by relating CO to body surface area (BSA), thus relating heart performance to the size of the individual

\[
CI = \frac{CO}{BSA}.
\]
CI (L/min/m²) and TPRI (mm Hg min L⁻¹ m⁻²), as independent variables. Kaplan–Meier analysis was employed to assess the time-to-IDME; comparison between strata was done by log-rank test. All statistical analyses were performed with SPSS version 11.5 (SPSS Inc.).

Results

Fourteen patients with end-stage renal disease (age 67 ± 15 years; 7 females) were studied during 30 dialysis sessions. The baseline characteristics of the study population are summarized in Table 1.

IDME

Dialysis treatment was complicated by IDH and muscle cramps in 4 and 8 out of 30 sessions, respectively (Table 2). The median time to intra-dialytic complication was 2.6 h. Continuous online haemodynamic monitoring revealed no differences in baseline BP and HR in patients without IDME as compared to those with muscle cramps or IDH. Age was higher in patients with cramps when compared to patients with no IDME, although the difference did not reach statistical significance (76 ± 12 vs 65 ± 14, Δ11, 95% CI: −23–1.2 years, P = 0.074). CI was significantly lower at the start of the dialysis treatment in patients with muscle cramps or IDH when compared to patients with no events (Table 2 and Figure 1). Ultrafiltration volume, although higher in patients experiencing cramps, did not differ statistically significant between groups.

A logistic regression model was built to test for an association between the occurrence of the composite endpoint IDME, with age, diabetes mellitus, ultrafiltration volume, mean arterial BP and CI (Table 3a and 3b) or TPRI (Table 4a and 4b) as predictors. The logistic regression models show that both a low baseline CI and a high baseline TPRI are independent predictors of IDME. The results were materially the same when ultrafiltration rate or ultrafiltration rate normalized to body weight was included instead of UFV in the model (data not shown). BMI did not differ between patients with and without IDME.

Time to IDME

Patients were stratified by tertiles for CI: three groups (CI low, n = 9, CI <1.97 L/min/m²; CI medium, n = 10, CI 1.97–2.51 L/min/m²; CI high, n = 10, CI >2.51 L/min/m²).

Table 2. Comparison of haemodynamic parameters observed during the first 30 min of haemodialysis in patients with no events, cramps and IDH (n = number of dialysis sessions)

<table>
<thead>
<tr>
<th>Variable</th>
<th>No events (n = 18)</th>
<th>Cramps (n = 8)</th>
<th>IDH (n = 4)</th>
<th>∆Cramps vs IDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFV (mL)</td>
<td>1662 ± 712</td>
<td>2243 ± 538</td>
<td>1375 ± 900</td>
<td>1375 ± 900</td>
</tr>
<tr>
<td>HR (l/min)</td>
<td>71 ± 14</td>
<td>71 ± 21</td>
<td>65 ± 6</td>
<td>65 ± 6</td>
</tr>
<tr>
<td>sBP (mm Hg)</td>
<td>119 ± 13</td>
<td>118 ± 13</td>
<td>120 ± 30</td>
<td>120 ± 30</td>
</tr>
<tr>
<td>dBP (mm Hg)</td>
<td>73 ± 11</td>
<td>71 ± 14</td>
<td>71 ± 19</td>
<td>71 ± 19</td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
<td>88 ± 12</td>
<td>86 ± 12</td>
<td>87 ± 23</td>
<td>87 ± 23</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>2.6 ± 0.6</td>
<td>2.0 ± 0.2</td>
<td>1.8 ± 0.2</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>TPRI (mm Hg min L⁻¹ m⁻²)</td>
<td>37.2 ± 11.7</td>
<td>46.0 ± 5.4</td>
<td>49.5 ± 13.3</td>
<td>49.5 ± 13.3</td>
</tr>
</tbody>
</table>

Mean ± SD; Δ (95% confidence intervals).

*P < 0.05.

*Measurements available for seven dialysis sessions.
In the groups CI low and CI medium, the mean time to IDME was significantly less compared to CI high. In CI high patients, no IDME occurred (Kaplan–Meier analysis; P < 0.002 by log-rank test; Figure 2).

Discussion

The present study was undertaken to investigate the relationship between haemodynamic indicators in the early phase of HD and subsequent IDME in chronic HD patients. Our results clearly demonstrate a relationship between proto-dialytic (i.e. during the early phase of dialysis treatment; in our study the first 30 min) low CI and high TPRI with subsequent episodes of IDME. Notably, parameters such as HR or BP did not indicate patients at risk for IDME. UFV did not differ significantly in patients with IDME as compared to patients with no IDME. The results were materially the same when ultrafiltration rate and ultrafiltration rate normalized to body weight. The multiple regression model indicates that diabetes mellitus was not correlated with IDME. This is surprising, given that both autonomic neuropathy and UFV are thought to play a major role in the pathophysiology of IDH and diabetes mellitus itself has previously been linked to HD-induced cardiac injury [22,36].

Cardiovascular disease is the leading cause of morbidity and mortality in MHD patients; however, there exists an increasing body of evidence to suggest that the responsible risk factors and underlying pathophysiological mechanisms

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient (β)</th>
<th>Standard error</th>
<th>P-value</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-1.256</td>
<td>8.811</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Age</td>
<td>0.035</td>
<td>0.050</td>
<td>0.482</td>
<td>1.036</td>
<td>0.939–1.142</td>
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<tr>
<td>DM</td>
<td>0.726</td>
<td>1.152</td>
<td>0.529</td>
<td>2.066</td>
<td>0.216–19.75</td>
</tr>
<tr>
<td>UFV</td>
<td>0.001</td>
<td>0.001</td>
<td>0.105</td>
<td>1.001</td>
<td>1–1.003</td>
</tr>
<tr>
<td>MBP</td>
<td>0.028</td>
<td>0.051</td>
<td>0.381</td>
<td>1.028</td>
<td>0.931–1.135</td>
</tr>
<tr>
<td>CI</td>
<td>-3.136</td>
<td>1.348</td>
<td>0.020</td>
<td>0.043</td>
<td>0.003–0.61</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
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<th>Standard error</th>
<th>P-value</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>4.723</td>
<td>2.468</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>UFV</td>
<td>0.001</td>
<td>0.001</td>
<td>0.158</td>
<td>1.001</td>
<td>1–1.002</td>
</tr>
<tr>
<td>CI</td>
<td>-3.100</td>
<td>1.186</td>
<td>0.045</td>
<td>0.004–0.460</td>
<td></td>
</tr>
</tbody>
</table>

Table 4a. Results of the logistic regression with IDME (yes/no) as the dependent variable and age (years), diabetes mellitus (yes/no), ultrafiltration volume (mL), mean arterial blood pressure (mm Hg) and total peripheral resistance index (mm Hg min L⁻¹ m⁻²) as explanatory variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient (β)</th>
<th>Standard error</th>
<th>P-value</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-8.116</td>
<td>7.536</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Age</td>
<td>0.039</td>
<td>0.048</td>
<td>0.418</td>
<td>1.039</td>
<td>0.947–1.141</td>
</tr>
<tr>
<td>DM</td>
<td>0.8</td>
<td>1.089</td>
<td>0.463</td>
<td>2.225</td>
<td>0.263–18.79</td>
</tr>
<tr>
<td>MABP</td>
<td>0.001</td>
<td>0.001</td>
<td>0.102</td>
<td>1.001</td>
<td>1–1.003</td>
</tr>
<tr>
<td>TPRI</td>
<td>-0.03</td>
<td>0.056</td>
<td>0.586</td>
<td>0.97</td>
<td>0.87–1.082</td>
</tr>
</tbody>
</table>

Table 4b. Results of the logistic regression with UFV and TPRI as explanatory variables

Our results clearly demonstrate a relationship between proto-dialytic (i.e. during the early phase of dialysis treatment; in our study the first 30 min) low CI and high TPRI with subsequent episodes of IDME. Notably, parameters such as HR or BP did not indicate patients at risk for IDME. UFV did not differ significantly in patients with IDME as compared to patients with no IDME. The results were materially the same when ultrafiltration rate and ultrafiltration rate normalized to body weight. The multiple regression model indicates that diabetes mellitus was not correlated with IDME. This is surprising, given that both autonomic neuropathy and UFV are thought to play a major role in the pathophysiology of IDH and diabetes mellitus itself has previously been linked to HD-induced cardiac injury [22,36].

Cardiovascular disease is the leading cause of morbidity and mortality in MHD patients; however, there exists an increasing body of evidence to suggest that the responsible risk factors and underlying pathophysiological mechanisms...
are different from those found in the general population [37]. Short intermittent HD, particularly when complicated by IDH, has been suggested as the significant cause of recurrent myocardial ischaemia with subsequent regional ventricular wall motion abnormalities in MHD patients [5,38]. This process is known as HD-induced myocardial ischaemia and is of considerable importance. A recent study showed that 50% of unaffected patients developed HD-induced regional wall motion abnormalities 12 months after initiation of dialysis therapy [36]. It is well established that repeated myocardial ischaemia leads to a chronic reduction in left ventricular function in non-dialysis patients which may even persist after normal perfusion has been restored [38–40]. Long-standing myocardial dysfunction following ischaemia (i.e. myocardial stunning) is just the beginning of a disease continuum where myocardial hibernation and fibrosis eventually lead to fixed segmental LV systolic dysfunction [39]. Recently, recurrent HD-induced myocardial stunning with cardiac fibrosis has become an acknowledged clinical conundrum in MHD patients, and intra-dialytic haemodynamic instability has been identified as an independent determinant of myocardial stunning [36,40–42].

In the light of these data, our findings suggest that hypotension-prone dialysis patients have an impaired cardiovascular reserve. The results indicate that compensatory haemodynamic mechanisms to maintain adequate circulation during dialysis (e.g. cardiac output and vasoconstriction) may be exhausted quite early in the course of an HD session, increasing the risk for the occurrence of IDME. This is in line with the notion that healthy persons can tolerate a decline in circulating blood volume of up to 20% before hypotension occurs, whereas in some dialysis patients, hypotension may take place with a substantially smaller decline in blood volume [43–45].

At present, the underlying pathophysiology of IDH is incompletely understood. During MHD, the fast removal of intravascular fluid, a slow refilling rate, an increase in body temperature, autonomic dysfunction, decreased plasma osmolality, impaired venous compliance, a decreased cardiac reserve, changes in serum potassium and calcium concentrations and even components of the dialysis fluid have all been discussed as contributors to haemodynamic instability [46–54]. Ultrafiltration leading to intravascular hypovolaemia is currently considered the main factor responsible for the acute fall of BP during HD treatment [55,56]. In our study, UFR did not differ significantly between patients with IDH and patients with no intra-dialytic events, suggesting the importance of alternative mechanisms. The multifactorial nature of IDH becomes evident when looking at the different mechanisms by which simple remedies restore BP during HD. For instance, in addition to plasma osmolality, plasma volume and dialysate temperature, more recent data suggest that the vasopres- sin plasma concentration plays a pivotal role in the treatment of IDH [57]. However, currently there is no consensus as to which of these strategies is most effective in preventing dialysis hypotension, which merely emphasizes the point made earlier that there is probably more than one single responsible pathophysiological mechanism. Considering the possible role of IDH in the development of cardiac injury in HD patients, the clinical relevance to identify patients at risk for IDME becomes evident.

Admittedly, our study suffers from some limitations: the relatively small number of patients encompasses a low power and the fact that all patients were Caucasians may limit the generalizability of the study. Additionally, it is conceivable that rapid fluid and electrolyte shifts in the initial phase of dialysis may interfere with ICG measurements; however, in an earlier study, we were able to show that cardiac output measurements determined by ICG and by an indicator dilution method (Transonic device) are highly correlated independent of the actual time passed during the dialysis treatment [33].

We have not systematically performed echocardiography as part of the study, and pre-dialysis hydration status was not determined with objective methods, such as bioimpedance. This would have been of great interest, since bioimpedance spectroscopy has recently been shown to aid physicians in achieving normohydration and better control of hypertension in HD patients [58,59]. However, it is clinical routine practice in our unit that patients are seen at each dialysis session by a nephrologist; none of the patients in our study had clinical signs of cardiac insufficiency and overhydration. Post-dialysis target weight (‘dry weight’) was determined clinically on a weekly basis and by employing echocardiography and chest X-ray studies as needed, but not less than twice a year. Clinically, no patient appeared hypovolaemic, making a low intravascular volume an unlikely cause for low CI.

Fig. 2. Kaplan–Meier estimation of event free time on dialysis. Patients were stratified by tertiles of cardiac index (CI) (log-rank test, P = 0.002).
Conclusion

Low CI and increased TPRI at the beginning of dialysis treatment are characteristics observed in HD patients with an increased risk for IDME. The results of our study indicate that compensatory mechanisms for maintaining adequate circulation during ultrafiltration are, in some patients, already exhausted in the early phase of HD. Employment of non-invasive haemodynamic monitoring, such as with the TFM, may aid early identification of patients at risk for IDME. The capability to record multiple key cardiovascular indicators may simultaneously facilitate the development of new preventive therapeutic strategies which may lead eventually to improved dialysis tolerance and patient outcomes.

Acknowledgements. The authors gratefully acknowledge the enthusiasm and collaboration of the staff at the Krankenhaus der Barmherzigen Brüder, Graz, in particular the help of Dr Waltraud Kirisits, Dr Herbert Loibner, Barbara Leitgeb, Helga Nitz and Martina Elsnig. Christofer Holland assisted the preparation of the manuscript.

Conflict of interest statement. The results presented in this paper have not been published previously in whole or part, except in abstract format. Falko Skrabal holds patents on the task force monitor used in the present study and he is co-founder of CNSystems which produces the instrument.

References

Prospective evaluation of aortic stenosis in end-stage kidney disease: a more fulminating process?

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Abstract

Background. We have previously demonstrated an increased rate of progression of aortic stenosis (AS) in patients with end-stage kidney disease (CKD 5D) compared to controls. We sought to follow prospectively a CKD 5D cohort with AS and determine major event-free survival. Follow-up was terminated once all CKD 5D subjects had undergone aortic valve replacement (AVR) or died. Our aim was to determine whether the increased rate of progression resulted in shorter major event-free (AVR or death) survival as compared to controls.

Methods. We re-matched our original CKD 5D cohort (n = 27) to a control cohort (n = 27) based on aortic valve area (AVA) at completion of the prior study. This was done...