Can Aortic Elastic Parameters be Used for the Diagnosis of Volume Overload in Patients with End Stage Renal Disease

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Key Words
End stage renal disease • Aortic elastic parameters • Volume overload • Body composition monitor • Bioimpedance spectroscopy

Abstract
Background: We aimed here to investigate hydration status by echocardiography in end stage renal disease (ESRD) patients. Methods: 25 ESRD patients [15 males; mean age: 54.0±16.6 years; 13 hemodialysis; 12 peritoneal dialysis] were considered eligible for this study. We also examined 29 healthy volunteers as a control group (17 males; mean age: 46.5±12.8 years). Body composition analysis using the bioimpedance spectroscopy technique was performed for volume overload diagnosis. The ratio of extracellular water (ECW) to height was used as volume indices. The aortic elastic parameters were calculated by echocardiography. A correlation analyses was performed between the ratio of ECW to height indicating the volume overload and the aortic elastic parameters e.g. Aortic strain (AS), Aortic distensibility (AD) and Aortic stiffness index (ASI). Results: The ratio of ECW to height that indicates volume overload in ESRD patients was considerably higher than that in the control group (10.25±1.98 L/m vs 8.66±1.22 L/m, p=0.001). There was a negative correlation between the ratio of ECW to height and AS and AD and a positive correlation between the ratio of ECW to height and ASI. Conclusion: Given the importance of the diagnosis and follow up of volume overload, the results show that aortic elasticity measurements, being easy to perform and replicate, can be used for this purpose.
Introduction

Cardiovascular morbidity and mortality are higher in patients with end-stage renal disease (ESRD) compared to normal population [1]. ESRD is associated with a variety of alterations in cardiac structure and function, including left ventricular (LV) dilatation, hypertrophy, systolic and diastolic dysfunction as related to volume overload [2, 3]. Aortic stiffness is also increased in patients with ESRD [4] and known to be associated with adverse cardiovascular outcomes and increased mortality such as those mentioned above [3-5]. The diagnosis and control of volume overload are of high significance in ESRD patients. Echocardiography is an established technique to estimate the risk for cardiovascular complications and a guide for treatment in patients with chronic renal failure [1-3]. However, it is not used for the diagnosis and follow up of volume overload.

Bioimpedance spectroscopy (BIS) represents a different approach to the assessment of fluid status [6-8]. The Body Composition Monitor (BCM) (Fresenius Medical Care, Germany) is a BIS device for clinical use, validated by isotope dilution methods [9], and reference body composition methods [10], and has been used in hemodialysis (HD) [11-14] and peritoneal dialysis (PD) [15, 16].

We aimed here to compare hydration status, as measured with BCM, and aortic elastic parameters, as measured by echocardiography, in ESRD patients.

Materials and Methods

Patients

Twenty-five ESRD patients (15 males; mean age: 54.0 ±16.6 years; 13 HD; 12 PD) were considered eligible for this study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Patients who were older than 18-years, on maintenance bicarbonate HD scheduled thrice weekly (12 hours/week) and prevalent patients undergoing PD for at least 6 months willing to participate in the study with a written informed consent were included. Exclusion criteria were the presence of pacemaker or defibrillator, artificial joints, pin or amputation, being scheduled for living donor renal transplantation, presence of serious life-limiting comorbid situations, like malignancy, uncontrollable infection, end-stage cardiac, pulmonary, or hepatic disease, pregnancy or lactating.

We also examined 29 volunteers which were chosen randomly with normal renal function as a control group (17 males; mean age: 46.5±12.8 years). Basic demographic data were collected for both study groups, including age, gender, presence of diabetes and the presence of traditional major cardiovascular risk factors (age, sex, hypertension, dyslipidemia, body mass index, and current smoking), and the year when the patient started dialysis. Patients were considered to have hypertension if they had previously known hypertension, or if they were on antihypertensive therapy, or if they had a systolic blood pressure of ≥140 mmHg and a diastolic blood pressure of ≥90 mmHg, which were calculated as the mean of two measurements taken on each arm. All volunteers underwent standard 2D M-mode and Doppler echocardiography and standard 12-derivation electrocardiogram.

Measurements

Measurement of overhydration. BIS was measured with the BCM from Fresenius Medical Care, Deutschland GmbH. Electrodes were placed on the right hand and foot on the site contra lateral to the arteriovenous fistula for HD patients mid week interdialytic day and in the morning with an empty abdomen for PD patients [17] with supine position. Two electrodes were dorsally placed on the hand in the metacarpophalangeal articulations and in the corpus, respectively, 5 cm apart. The pair on the foot was located in the metatarso-phalangeal and in the articulation, 6 cm apart. The BCM analyses total body electrical impedance to an alternate current (0.2 mA) with fifty different frequencies (5-1000 kHz). The volume of extracellular water (ECW) is calculated from electrical resistances determined by BCM. The ratio of ECW to height was used as volume indices.
Echocardiographic examination. Standard echocardiographic examinations were performed using a Vingmed Vivid System 5 (General Electric, Horten, Norway) device. A 2.5 MHz probe and a 2.5-3.5 MHz probe was used for the Doppler measurements and for tissue Doppler measurements respectively. All measurements were averaged from three cardiac cycles. 2D echocardiographic measurements were performed according to the standards outlined by the American Society of Echocardiography [18]. LV dimensions and wall thickness were obtained from the parasternal long axis with an M-mode cursor positioned just beyond the mitral leaflet tips, perpendicular to the long axis of the ventricle. LV end-diastolic diameter (LVEDD) and end-systolic (LVESD) diameter, thickness of the interventricular septum (IVS) and posterior wall of the left ventricle (PW) were measured. LV ejection fraction was calculated according to the Simpson method [19]. Mitral inflow velocities were evaluated by pulse-wave Doppler echocardiography with the sample volume placed at the tip of the mitral leaflets from the apical four-chamber view. Diastolic peak early (E) and peak late (A) transmittal flow velocity, peak E to peak A velocities (E/A), and deceleration time of peak E velocity (EDT) were measured.

The LV-pulsed tissue Doppler imaging (TDI) was performed in the apical four-chamber view using a 5-mm pulsed Doppler sample volume with as minimum optimal gain as possible to obtain the best signal-to-noise ratio. Care was taken to align the echo image so that the annular motion was parallel to the TDI cursor. Spectral pulsed wave Doppler signal filters were adjusted until a Nyquist limit of 15–20 cm/s was reached. The monitor sweep speed was set at 50–100 mm/s to optimize the spectral display of myocardial velocities. The sample volume was placed at the junction of the LV wall and the septal annulus from the four-chamber view sequentially. The myocardial peak early (Em) velocities were obtained from the septum of the left ventricle. All echocardiographic measurements were performed by the same observer. The ratio of E/Em for septal segment was measured. While echocardiographic examination was performed to obtain blood pressure data required to calculate the aortic elastic parameters, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured simultaneously using a mercury sphygmomanometer and heart rate was simultaneously recorded by an electrocardiogram. All the measurements were performed at midweek interdialytic day for HD patients, and in the morning with an empty abdomen for PD patients.

Aortic elasticity
The parasternal long axis view was modified and the ascending aorta was monitored. M-mode echocardiographic tracings of the aorta were recorded at a level of 3 cm above the aortic valve. From the tracings recorded, systolic diameter of the ascending aorta (AoS) and diastolic diameter of the ascending aorta (AoD) were obtained. AoS was measured at the time of the full opening of the aortic valve and AoD was measured at the peak of QRS. At least three subsequent measurements were performed for each participant and the average of these measurements was calculated. The indices of aortic elastic properties, aortic strain (AS), aortic distensibility (AD) and aortic stiffness index (ASI), were calculated using the following formula [20]:

\[\text{Aortic Strain} \% = 100 \times \frac{(\text{AoS} - \text{AoD})}{\text{AoD}}\]

\[\text{Aortic Distensibility} \ (\text{cm}^2 \times \text{dyn}^{-1} \times 10^{-6}) = \frac{(2 \times \text{Aortic Strain})}{(\text{SBP} - \text{DBP})}\]

\[\text{Aortic Stiffness Indeks} = \ln \left(\frac{\text{SBP}}{\text{DBP}}\right) \times \frac{(\text{AoS} - \text{AoD})}{\text{AoD}}\]

Statistical analysis
Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) for Windows (version 15; SPSS Inc., Chicago, IL, USA). The quantitative variables of the study were expressed as mean and standard deviation. Categorical variables were recorded using frequency and percentage. ROC (Receiver Operating Characteristic) curve analysis was used to determine the best cutoff points for the best value that can distinguish between the cases with and without volume overload. To determine the differences between the two groups, variables were evaluated using the Mann–Whitney U-test. Spearman’s correlation analysis was performed to examine the relationship between continuous variables and outcomes. In this study, a p-value of <0.05 was considered to be statistically significant.

Reproducibility
Intraobserver variability was calculated as the difference in two measurements of the same patient by one observer divided by the mean value. Intraobserver variability was less than 5% for all aortic elasticity measurements.
Results

The clinical characteristics and demographics of the patient and control groups were similar except for renal functions (Table 1). Table 2 compares bioimpedance, biochemical and echocardiographic data. The mean vintage of dialysis was 3.76±2.31 years for HD patients and 4.71±2.81 years for PD patients. ESRD patients had higher left atrial and aortic diameters as compared to the control group (3.85±0.65 mm vs 3.53±0.31, p=0.006 and 3.27±0.48 vs 3.03±0.38, p=0.035). Both groups had normal LV ejection fraction. The patient group had lower values for aortic strain and aortic distensibility and higher aortic stiffness index as compared to the control group (Table 2). Moreover, LV diastolic dysfunction was found in the patient group (E/A was 0.93±0.41 and E/E' was 13.8±4.37). In the patient group, clinical, demographic, bioimpedance, biochemical and echocardiographic parameters of the patients undergoing HD and PD were almost same. (Table 3). The HD group only had greater end systolic and end diastolic aortic diameters as compared to the PD group.

The ratio of ECW to height that indicates volume overload in ESRD patients was considerably higher than that in the control group (10.25±1.98 L/m vs 8.66±1.22 L/m, p=0.001). ROC analysis was performed to determine the threshold value that can predict volume overload. In the ROC curve analysis, sensitivity and specificity were 76% and 75.9%, respectively, when an ECW/H ratio cutoff point of 9.44 was used to distinguish between the groups with and without volume overload (Fig. 1). A correlation analysis was performed...
Table 3: Data of the patient group

<table>
<thead>
<tr>
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<th>HD (n=13)</th>
<th>PD (n=12)</th>
<th>P</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>60.5±14.5</td>
<td>47.0±16.5</td>
<td>NS</td>
</tr>
<tr>
<td>Dialysis vintage (years)</td>
<td>3.76±2.31</td>
<td>4.71±2.81</td>
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</tr>
<tr>
<td>Male (n)</td>
<td>10</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.7±3.6</td>
<td>27.2±9.8</td>
<td>NS</td>
</tr>
<tr>
<td>HT (n)</td>
<td>8</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>DM (n)</td>
<td>7</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>DL (n)</td>
<td>0</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Current smoker (n)</td>
<td>2</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>145.3±29.5</td>
<td>133.0±27.9</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72.0±11.8</td>
<td>73.4±16.4</td>
<td>NS</td>
</tr>
<tr>
<td>HR (1/min)</td>
<td>76±11</td>
<td>81±13</td>
<td>NS</td>
</tr>
<tr>
<td>IVS (mm)</td>
<td>1.23±0.30</td>
<td>1.15±0.27</td>
<td>NS</td>
</tr>
<tr>
<td>PW (cm)</td>
<td>1.23±0.30</td>
<td>1.14±0.23</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>4.73±0.35</td>
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<td>NS</td>
</tr>
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<td>LVESD (cm)</td>
<td>2.83±0.40</td>
<td>2.60±0.64</td>
<td>NS</td>
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<tr>
<td>LA (cm)</td>
<td>4.07±0.62</td>
<td>3.63±0.64</td>
<td>NS</td>
</tr>
<tr>
<td>AOS (cm)</td>
<td>3.50±0.33</td>
<td>3.03±0.51</td>
<td>p=0.008</td>
</tr>
<tr>
<td>AOD (cm)</td>
<td>3.37±0.36</td>
<td>2.90±0.55</td>
<td>p=0.03</td>
</tr>
<tr>
<td>AS (%)</td>
<td>4.23±2.50</td>
<td>4.71±3.2</td>
<td>NS</td>
</tr>
<tr>
<td>AD (cm² x dyn⁻² x 10⁶)</td>
<td>1.43±1.17</td>
<td>2.1±2.04</td>
<td>NS</td>
</tr>
<tr>
<td>ASI</td>
<td>4.03±0.74</td>
<td>3.88±0.86</td>
<td>NS</td>
</tr>
<tr>
<td>EDT (ms)</td>
<td>269±66</td>
<td>268±43</td>
<td>NS</td>
</tr>
<tr>
<td>E/A</td>
<td>0.91±0.41</td>
<td>0.95±0.42</td>
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<td>E/E'</td>
<td>14.05±5.47</td>
<td>13.54±2.97</td>
<td>NS</td>
</tr>
<tr>
<td>EF (%)</td>
<td>57.6±5.4</td>
<td>59.8±5.7</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinin (mg/dl)</td>
<td>8.16±2.15</td>
<td>9.48±2.14</td>
<td>NS</td>
</tr>
<tr>
<td>ECW/H (L/m)</td>
<td>10.30±2.57</td>
<td>10.21±1.35</td>
<td>NS</td>
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</table>


Fig. 1. ROC (Receiver Operating Characteristic) curve analysis of the patients group for determine the threshold value that can predict volume overload.

between the ratio of ECW to height indicating the volume overload and the aortic elastic parameters AS, AD and ASI. There was a negative correlation between the ratio of ECW to height and AS and AD and a positive correlation between the ratio of ECW to height and ASI in patient group (Table 4). However, there was a positive correlation between the ratio of ECW to height and AS and AD and a negative correlation between the ratio of ECW to height and ASI in control group (Table 4, Fig. 2).
Discussion

The aorta plays an important role in the physiology of cardiovascular system. One of the most important physiological roles of the aorta is the capability to store blood ejected by the heart and to transfer this storage into the peripheral circulation during systole (Windkessel function) [21]. Elastic properties of the aorta play a major role at this point. Aortic stiffness indicates impaired elastic properties of the aorta [22]. Aortic stiffness is increased in patients with end-stage renal disease [4] and known to be associated with adverse cardiovascular outcomes and increased mortality [5]. Aortic stiffness is regarded as an important parameter reflecting early changes in vascular structure [23]. The mechanisms and time frames for the development of arterial stiffness in ESRD patients are unclear but may include traditional cardiovascular risk factors such as dyslipidemia and hypertension. Increased stiffness was shown to be largely influenced by the vascular calcifications [4]. Studies evaluating vascular calcification in ESRD patients showed that vascular calcification is an active process like atherosclerosis, and related with trans-differentiation of vascular smooth muscle cells to osteoblast/osteocyte-like cells, activation of osteoblastic transcription factors, and expression of bone matrix proteins [24, 25]. Other potential pathophysiological mechanisms by which renal dysfunction increases aortic stiffness include the detrimental effect of oxidative stress and inflammation, as well as elevated plasma levels of asymmetric dimethylarginine and homocysteine on endothelial function [26]. Chronic volume overload may also induce alterations of mechanical forces and lead to changes in the geometry and composition of the vessel walls in ESRD patients. [27]. In this study, the aortic elastic parameters, AS and AD, were lower and ASI was higher in ESRD patients as compared to the control group, which is consistent with the literature.

Achieving a normal hydration state is one of the primary objectives in HD and PD treatments. The abnormal state of overhydration has been related to arterial hypertension, signs and symptoms of pulmonary and peripheral oedema, heart failure, left ventricular hypertrophy, and other adverse cardiovascular effects [28]. It has also been shown to be likely to cause arterial stiffness in this study. It was described that hydration state is an important independent predictor for mortality in chronic HD patients [11]. Therefore, the diagnosis and control of volume overload are of high importance in ESRD patients. In ESRD patients, the “gold standard” methods for measuring body water, such as deuterium (total body water) and sodium bromide (extracellular water), are laborious and cannot be used in clinical practice [29]. In most centers, the dry weight is determined based on clinical findings and is defined as the lowest weight a patient can tolerate without the development of symptoms such as hypotension, and cramp, which are complications experienced during dialysis. However, this method may not always yield reliable results that can guide treatment. Bioelectrical impedance analysis is a promising method for the objective assessment and monitoring of hydration in patients on ESRD. Whole-body bioimpedance spectroscopy has been shown to be as precise as the gold standard reference methods. The combination of this technology with the BCM model described in Chamney et al. [30] allows for the first time a target normohydration to be calculated. In this study, the ratio of ECW to height was used.

Table 4: Speaman’s correlation analysis with the ratio of ECW to height

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<tr>
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<th>Patients</th>
<th>Controls</th>
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<tbody>
<tr>
<td></td>
<td>R</td>
<td>P</td>
</tr>
<tr>
<td>AS (%)</td>
<td>-0.628</td>
<td>0.001</td>
</tr>
<tr>
<td>AD (cm² x dyn⁻¹ x 10⁴)</td>
<td>-0.613</td>
<td>0.001</td>
</tr>
<tr>
<td>ASI</td>
<td>0.630</td>
<td>0.001</td>
</tr>
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</table>

AS: aortic strain, AD: aortic distensibility, ASI: aortic stiffness index

Fig. 2. Scatter plots of the correlation analysis between the ECW/H ratio and aortic elastic parameters in both patient and control groups.
for the detection of volume overload since the increased volume does not affect intracellular water but only ECW. Previously, it was shown that the ratio of ECW to height measured by bioimpedance could be used as a volume parameter and was increased in ESRD patients [15]. In the present study, the ratio of ECW to height was higher in ESRD patients as compared to the control group, which indicates volume overload in the patient group.

A decrease in AS and AD and an increase in ASI indicate impaired aortic elastic functions. In our study, volume overload was found to be negatively correlated with AS and AD and a positive correlation was found between volume overload and ASI in the group of patients with impaired aortic elastic functions. In the control group with preserved aortic elastic functions AS and AD were increased, while ASI was decreased. This inverse relationship found in the patient and control groups was considered to be caused by the difference in aortic elastic properties. In individuals without impairment in elastic functions, increased volume causes stretching of arterial walls, resulting in an increase in AS and AD and a decrease in ASI by affecting aortic diameters without influencing pulse pressure significantly (since adequate stretching occurs in systole). In patients with end-stage renal disease, however, since the elastic functions are impaired and due to arterial stiffness, increased volume will not cause a difference in the aortic diameters (due to inadequate stretching during systole) and will lead to an increase in the pulse pressure. This in turn will lead to impairment in aortic elastic parameters (decrease in AS and AD and increase in ASI).

Study Limitations

Several limitations of this study should be concerned. First, the most important limitation of this study was the small number of patients. Secondly, invasive techniques were not used to assess blood pressure. Blood pressure was measured by cuff sphygmomanometry of the brachial artery. However, Stefanadis et al showed that aortic stiffness determined by the echocardiographic method was closely related to that obtained by directly invasive measurements and suggested that aortic distensibility could be obtained noninvasively with a high degree of accuracy [32]. Additionally, we used indirectly measured brachial artery blood pressure instead of intraaortic pressure for the calculation of stiffness and distensibility indices. In the same study, there was a high correlation between aortic and brachial blood pressures [32]. Another limitation is that aortic elastic parameters are affected by many factors. In the evaluation of the patient, it may be difficult to determine whether impaired aortic elastic parameters are caused by volume load or additional comorbid causes. Therefore, it may be more useful in the follow-up of diagnosed volume overload. Furthermore, this study is of cross sectional design. We did not investigate the effects of the control of volume overload on aortic elasticity in the long term. Further long term studies with large patient populations are warranted.

Conclusion

In this study, a relationship was found between volume overload and aortic elastic parameters, an important indicator of cardiovascular adverse events, which suggests that volume overload is one of the causes of aortic stiffness and that the control of volume overload can prevent aortic stiffness. The major cause of death in ESRD patients is cardiovascular disease [31] and volume overload is an important cause of adverse cardiovascular events [28]. Thus, a strict follow up of volume overload is of high importance in ESRD patients. As volume overload increases so does aortic stiffness. Though being a result of volume overload, aortic stiffness can be used as an indicator of volume overload. Given the importance of the diagnosis and follow up of volume overload, the results show that aortic elasticity measurements, being easy to perform and replicate, can be used for this purpose.
Conflict of Interests

There is no conflict of interest.

References


