Influence of Preload Reduction on Tei Index and Other Doppler Echocardiographic Parameters of Left Ventricular Function

Silvio Henrique Barberato e Roberto Pecoits Filho
Centro de Ciências Biológicas e da Saúde e Pontifícia Universidade Católica do Paraná - Curitiba, PR - Brazil

OBJECTIVES
To assess the influence of preload reduction by hemodialysis on Doppler Tei Index of myocardial performance and other parameters of cardiac function.

METHODS
The Tei index and left ventricular (LV) systolic and diastolic function parameters were estimated, before and after a single hemodialysis session. Only subjects who were in sinus rhythm, without history of coronary artery disease, and no evidence of cardiac valve disease and pericardial effusion were included in the study.

RESULTS
Fifteen patients (8 men, mean age 53 ± 14 years) completed the study. After an ultrafiltration of 2,2 ± 1,1 liters, peak mitral E velocity decreased (p< 0,05) and A velocity remained unchanged (p = ns), resulting in reduction of E/A ratio (p< 0,01). The Tei index increased (from 0,57 ± 0,07 to 0,65 ± 0,09, p< 0,01) because of significant prolongations in isovolumetric relaxation time (from 101 ± 14 to 113 ± 17 ms, p< 0,01) and ejection time (from 271 ± 22 to 252 ± 22, p< 0,05). The isovolumetric contraction time did not vary (p = ns). There was no change in diastolic tissue Doppler parameters, while systolic velocities increased (p< 0,05).

CONCLUSION
The Tei index was affected by hemodialysis-induced preload alterations, as well as other mitral infl ow Doppler-derived parameters. The diastolic parameters of mitral annulus Doppler tissue were independent of preload, while systolic velocities suggested improved systolic function.

KEY WORDS
Renal dialysis, echocardiography, Doppler, ventricular function, left.

Mailing Address: Silvio Henrique Barberato • Rua Saint Hilaire, 122/203, 80240-140 – Curitiba, PR - Brazil
E-mail: silviohb@cardiol.br
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Patients with chronic renal failure (CRF) on maintenance hemodialysis (HD) experience a series of metabolic and hemodynamic abnormalities that predispose to anatomic and functional change in myocardial performance\(^1\). Thus, left ventricular (LV) hypertrophy, a geometric change independently predictive of mortality\(^2\)\(^-\)\(^6\), is usually accompanied by diastolic dysfunction. Left ventricular systolic dysfunction seems to be less frequent\(^4\)\(^-\)\(^6\), although it also adds prognostic value\(^6\).

Tei et al described a Doppler echocardiographic myocardial performance index combining time intervals related to systolic and diastolic function that reflects global cardiac function\(^7\). The Tei index is defined as the sum of isovolumetric contraction time (IVCT) and isovolumetric relaxation time (IVRT) divided by left ventricular ejection time (ET). Numerous studies have demonstrated its clinical value as a sensitive indicator of the severity of myocardial dysfunction\(^8\)\(^-\)\(^10\) and also a prognostic predictor in several heart conditions\(^11\)\(^-\)\(^14\). Theoretically, this index presents a series of advantages that can be effectively used to evaluate cardiac function of CRF patients on hemodialysis. It is easily obtained and reproducible, regardless of ventricular cavity geometry\(^11\); in addition, it is not affected by heart rate and blood pressure\(^8\). However, human\(^16\)\(^,\)\(^17\) and animal\(^18\)\(^,\)\(^19\) studies have shown the sensitivity of the index to loading manipulations. During hemodialysis, there is a sudden decrease in plasma volume secondary to ultrafiltration, thereby constituting an interesting clinical model of preload reduction.

A number of studies have analyzed the influence of preload reduction by hemodialysis in isolated Doppler echocardiographic indices of systolic or diastolic function, evaluated by several parameters, such as ejection fraction\(^20\) and other contractility indices\(^21\), mitral inflow velocities and intervals by pulsed Doppler\(^22\)\(^-\)\(^25\), mitral annular velocities by tissue Doppler\(^26\)\(^-\)\(^28\), and left atrial volume\(^29\). Nevertheless, few data exist about preload influence on the Tei index in a clinical condition of rapid changes in blood volume. This study aims at evaluating the effect of acute preload reduction mediated by a single hemodialysis session on the Tei index, as well as on other systolic and diastolic function indices provided by Doppler echocardiography, investigating whether these parameters depend on intravascular volume.

**METHODS**

Nineteen CRF patients referred for transthoracic echocardiography (pre-renal transplantation assessment) were studied. These patients had been on maintenance hemodialysis for at least one month at the Nephrology Service of our institution (four-hour sessions, three times a week). Inclusion criteria were clinically stable patients in sinus rhythm, with no history of coronary artery disease (evaluated by medical chart review and detailed medical history), nor evidence of significant valvular heart disease (any degree of mitral or aortic stenosis; more than mild mitral or aortic insufficiency) or pericardial effusion. The project was approved by the institution’s Ethics Committee, and all patients gave a written informed consent to participate in the study.

Dry weight (volume to be removed by ultrafiltration) was estimated based on clinical signs of hydration and blood pressure behavior during the session, together with electrical bioimpedance\(^30\). Hemodialysis machines used were Altra Touch (Althin, Miami, Florida, FL, USA) equipped with cellulose-acetate dialyzers regulated to a blood flow rate of 200mL/min and a dialysate flow rate between 300 and 400 mL/min.

Systolic and diastolic blood pressure, heart rate, height, and body weight were measured before and after HD. Ultrafiltrate was estimated by the difference between pre- and post-hemodialysis body weight, considering 1 kg = 1 liter, as in previous HD studies\(^24\)\(^-\)\(^26\). Body surface area was calculated according to Mosteller’s simplified formula \((0.20247 \times \text{weight}^{0.425} \times \text{height}^{0.725})\)\(^31\). The body mass index was calculated by dividing weight in kilograms by height in meters squared.

Echocardiograms were performed immediately before and approximately 30 minutes after the HD session by a single level-3 cardiologist-echocardiographer blind to clinical data, in compliance with guidelines established by the American College of Cardiology/American Heart Association task-force\(^32\). All examinations were conducted using an HDL 3000 echocardiograph (ATL-Philips Ultrasound Systems, Bothell, Washington, EUA) equipped with a 2.5-MHz transducer, with patients in left lateral decubitus. The usual sections were used to allow a thorough M-mode, two-dimensional, and Doppler echocardiography study (pulsed, continuous, color, and tissue) before and after the session. The following parameters were derived from M-mode measurements: left atrial anteroposterior diameter, interventricular septal and posterior wall thickness during diastole, LV end-diastolic and end-systolic dimensions. Left atrium was considered enlarged when it was > 40 mm, and LV was considered dilated when end-diastolic diameter was > 55 mm. Left ventricular mass was calculated using Devereux’s formula according to the Penn convention\(^33\) and indexed to body surface area. Left ventricular hypertrophy was diagnosed when the LV mass index was greater than 134 and 110 g/m\(^2\) of body surface for men and women, respectively. Left ventricular fractional shortening was calculated from M-mode-derived diameters, as well as ejection fraction by the cube method\(^35\). Left ventricular systolic dysfunction was diagnosed when ejection fraction was < 65%. Mitral inflow velocities were measured in the apical four-chamber view with pulsed the Doppler sample placed between the leaflet tips of the mitral valve\(^36\); at this time patients were instructed to hold their breath. Rapid early filling (E) and atrial contraction (A) velocities, as well as the E/A ratio and IVRT, were determined. The Tei index was calculated using the formula a-b/b, where
a = mitral closure-to-opening interval (time interval from cessation to onset of mitral inflow); and b = ET (aortic flow ejection time, obtained at the LV outflow tract). Isovolumetric contraction time (IVCT) was determined from the following subtraction: a - (IVRT + ET).

Mitral annular velocities measured by tissue Doppler were recorded in the apical four-chamber view, with a 2- to 4 mm sample volume placed at the junction of the LV lateral wall with the mitral annulus. For optimal recording of low-velocity and high-amplitude myocardial signals, both gain and filter were set as low as possible. Both early (E') and late (A') diastolic mitral annular velocities were obtained, in addition to E'/A' and E/E' ratios. Systolic mitral annular velocity (S) was also recorded for longitudinal contractile function. All Doppler echocardiographic measurements represented an average of three heart cycles.

Left ventricular diastolic function was categorized based on the interpretation of both mitral inflow Doppler and tissue Doppler indices in four patterns: normal (grade 0), abnormal relaxation (grade I), pseudonormal (grade 2), and restrictive (grade 3). With the E/A ratio < 1, it was classified as grade I; while with the E/A ratio > 2 it was considered grade 3. In the discrimination between true normal and pseudonormalized pattern, the concomitant analysis by mitral annular tissue Doppler indices in four patterns: normal (grade 0), abnormal relaxation (grade I), pseudonormal (grade 2), and restrictive (grade 3) as percentage changes from baseline conditions. After ultrafiltration, mitral inflow E-wave decreased (94 ± 22 to 78 ± 26 cm/s, p < 0.05), but mitral flow A-wave remained unchanged (100 ± 34 to 103 ± 30 cm/s, p = 0.6), resulting in a significant decrease in the E/A ratio (1.1 ± 0.5 to 0.8 ± 0.3, p < 0.01). The Tei index increased (0.57 ± 0.07 to 0.65 ± 0.09, p < 0.01) due to IVRT prolongation (101 ± 14 to 113 ± 17 ms, p < 0.01) and ET shortening (271 ± 22 to 252 ± 22, p < 0.05). The IVCT remained unaltered (53 ± 9 to 50 ± 13 ms, p = 0.3).

Tissue Doppler-derived diastolic parameters showed no significant change after hemodialysis: E' (8.5 ± 0.9 to 8.0 ± 2 cm/s, p = 0.3), A' (12.4 ± 2 to 11.9 ± 2 cm/s, p = 0.05). The IVCT remained unaltered (53 ± 9 to 50 ± 13 ms, p = 0.3).

Table 2 shows the means of several Doppler echocardiographic indices, including the Tei index and its components, before and after HD session, as well as percentage changes from baseline conditions. After ultrafiltration, mitral flow E-wave decreased (94 ± 22 to 78 ± 26 cm/s, p < 0.05), but mitral flow A-wave remained unchanged (100 ± 34 to 103 ± 30 cm/s, p = 0.6), resulting in a significant decrease in the E/A ratio (1.1 ± 0.5 to 0.8 ± 0.3, p < 0.01). The Tei index increased (0.57 ± 0.07 to 0.65 ± 0.09, p < 0.01) due to IVRT prolongation (101 ± 14 to 113 ± 17 ms, p < 0.01) and ET shortening (271 ± 22 to 252 ± 22, p < 0.05). The IVCT remained unaltered (53 ± 9 to 50 ± 13 ms, p = 0.3).

Table 1 - Clinical and echocardiographic characteristics of the population studied

<table>
<thead>
<tr>
<th>Parameters</th>
<th>n = 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53 ± 14</td>
</tr>
<tr>
<td>Men</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>Length of time on hemodialysis (months)</td>
<td>15 (3-96)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24 ± 6</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.5 ± 2.5</td>
</tr>
<tr>
<td>Cause of CRF</td>
<td></td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>Hypertensive glomerulosclerosis</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>SAH and DM</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Anti-hypertensive drugs</td>
<td></td>
</tr>
<tr>
<td>Angiotensin II-converting enzyme inhibitor</td>
<td>4 (27%)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Echocardiographic anatomic changes</td>
<td></td>
</tr>
<tr>
<td>Hypertrophy</td>
<td>15 (100%)</td>
</tr>
<tr>
<td>LV dilation</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>LA dilation (M-mode)</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>Mitral valve calcification</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Aortic valve calcification</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Mitral and aortic valve calcification</td>
<td>4 (27%)</td>
</tr>
</tbody>
</table>
DISCUSSION

Hemodialysis patients constitute an interesting group for assessing reduced preload effects on cardiac function parameters by Doppler echocardiogram. This study investigated the effects triggered by HD on the Tei index, which reflects global myocardial function, and on systolic and diastolic function indices separately, in a group of CRF patients waiting for renal transplantation. Fluid removal resulted in a mean weight reduction of 2.2 Kg (or 2.2 liters of body water), causing a decline in intravascular volume and a drop in preload, as may be inferred by reduced LV dimensions. The decrease in circulating plasma volume led to changes in the Tei index, demonstrating that it is affected by load conditions.

Diastolic indices derived from mitral inflow, including E-wave, E/A ratio, and IVRT varied significantly, similar to other studies using HD as clinical model of preload reduction. It is known that pulsed Doppler-derived velocities are extremely volume-dependent, and the rapid drop in filling pressure caused by HD may expose to a pseudonormalization of mitral flow. Criteria for mitral flow pseudonormalization were followed in six patients before HD, five of whom showed abnormal relaxation on standard Doppler after hemodialysis. We thus confirm that HD does not affect left ventricular diastolic function adversely, but rather induces changes that depend on the sensitivity of mitral Doppler parameters to preload variations, sometimes “unmasking” a preexistent diastolic dysfunction.

As this study demonstrates, the role of mitral annular tissue Doppler as a method to assess the relatively independent diastolic function of preload should be underscored, as it was also demonstrated in this study. No change in E’ and A’ velocity was found with the average amount removed by ultrafiltration in our group, a finding similar to that reported in previous publications. Other authors who used high-flow HD and/or greater blood volume loss, or who included myocardial ischemia patients, observed variations in mitral annular velocities after HD. It seems reasonable to say that E’ is little affected by HD, compared to E. The HD effect on E’ may be ignored as long as no excess fluid is removed.

Pulsed-wave Doppler-derived systolic indices showed that IVCT remained unchanged and ET shortened significantly. Because of the combined changes in mitral flow intervals (prolonged IVRT and shortened ET), there was significant Tei index variation, which increased with preload reduction. An alternative analysis could propose a decrease in myocardial performance after the HD session due to systolic function deterioration, as may be suggested by the reduced ventricular ejection fraction.

Some arguments may be presented against this hypothesis. Firstly, we sought to exclude factors that could
lead to an acute decrease in myocardial performance, such as valvular heart disease, pericardial disease, or myocardial ischemia. Although the presence of coronary heart disease was not checked by means of other non-invasive or invasive tests, the degree of plasma volume depletion during our experiment was probably within certain “physiological” ranges, since it was not followed by significant change in heart rate and blood pressure. The occurrence of arterial hypotension could have led to reflex tachycardia, subsequent ischemia, and a decrease in LV function parameters.

Secondly, the assumption that decreased ET may indicate a decline in systolic function is contradicted by the increase observed in ejection fraction (radial myocardial contractile function), and especially in S-wave velocity measured by mitral annular tissue Doppler (longitudinal contractile function). The ET shortening mechanism is likely to be related to the decrease in blood volume after HD, which reduces end-diastolic volume and LV stroke volume. It is known that HD may induce a dissociation between changes in ventricular filling and in contractile state. Thus, despite the ET abbreviation secondary to a decrease in left ventricular filling, contractile function apparently improved, probably due to uremic toxin removal. This effect is achieved by an isolated ultrafiltration that antagonizes the Frank-Starling mechanism and does not remove the toxins that depress myocardial function. Therefore, while contractile function indices improved, there was a paradoxical prolongation of the Tei index.

These findings corroborate the known sensitivity of systolic intervals to preload variations, including ejection time. The HD effects on LV systolic performance vary and seem to depend partly on ventricular volumes and contractile function prior to dialysis. Alpert et al suggested that LV systolic function only improves after HD session in patients with previous systolic dysfunction, and that is does not change significantly in individuals with normal function. It is worth noting that this study used mean velocity of circumferential fiber shortening (M-mode-derived) as the index for systolic function, rather than ejection fraction. On the other hand, a small study (ten patients) using the same method to evaluate a pediatric HD population suggested a real improvement in myocardial contractile function in that group.

In a more recent study performed on 128 chronic renal disease patients with normal baseline systolic function, no change was found in percent shortening and ejection fraction with HD, but the primary purpose of the article was to study diastolic function, and presence of coronary artery disease was not an exclusion criterion. Our group showed improvement both in ejection fraction and systolic annular velocity measured by tissue Doppler. With regard to ejection fraction, this improvement could be suggested by the preload influence itself on the index, as demonstrated previously. Alternatively, the inclusion of three patients with reduced systolic dysfunction at baseline, a subgroup in which mean ejection fraction increase after dialysis was 17%, could theoretically have created a bias for the overall result of the group. However, there was also a significant and consistent increase in the S-wave, which is in keeping with a previous publication that pointed to improvement in myocardial systolic velocities of CRF patients after HD.

It seems reasonable to infer that the S-wave increase should represent a real improvement in contractility of longitudinal myocardial fibers, since tissue Doppler is relatively preload-independent, and the amount of induced-volume variation in our group failed to produce changes in mitral annular diastolic velocities. The possibility of studying not only radial myocardial contractility but also longitudinal systolic function using novel echocardiographic techniques, such as tissue Doppler and myocardial strain, opens a new path to research aimed at understanding heart performance under load variation.

A similar study performed by Koga et al also sought to evaluate the impact of HD-induced preload alterations on the Tei index. Evaluating 32 patients with mean age of 72 ± 9, on HD for 40 ± 35 months and showing normal ejection fraction, these authors found a significant decrease in E velocity and E/A ratio, associated with an increase in the Tei index (due to IVRT + IVCT prolongation and ET shortening). It is interesting to note that, in evaluating two groups according to the amount of weight loss, whether ≥ 1.5 kg or <1.5 kg, only the first group showed changes in the Tei index. Analysis of the group as a whole revealed no changes in LV dimension and volume (weight loss 1.8 ± 0.7 kg), and ejection fraction remained unaltered after hemodialysis.

Our population consisted only of patients with myocardial hypertrophy and diastolic dysfunction, in addition to three patients with systolic dysfunction. This may explain baseline differences in the Tei index of the populations evaluated (0.57 ± 0.07 vs 0.42 ± 0.16 in the Japanese study). In our group, weight loss was greater (12.2 ± 1.1 kg), allowing a more expressive reduction in circulating volume and thus relieving volume overload and resulting in different ejection fraction response. Therefore, the Tei index showed to be affected by preload reduction in a mixed sample as well, in patients with systolic and diastolic dysfunction, as had already been demonstrated in the population with normal systolic function in the Japanese study. This variation seems to depend on the volume removed, regardless of baseline systolic function.

The main limitations of our study were the small number of patients, the echocardiographer failure to perform off-line measurements, and the fact that he was not blind to pre- or post-HD time. In regard to sample size, it is important to note that the small "n" was partly due to strict selection criteria and that this did not prevent a high statistical power to be achieved for Tei index variation (power = 0.99). Due to logistic issues, a blind study was not possible, but that limitation...
has been present in other dialysis studies as well. Moreover, the fact that all the examinations were performed by a single echocardiographer contributed to reduce record variability.

Our results showed that the Tei index is affected by reduction in circulating blood volume induced by HD, raising its value, which could be misinterpreted as a decrease in myocardial performance. We concluded that, as with other parameters derived from mitral inflow Doppler, this index may be affected by preload changes mediated by HD. Among the other parameters evaluated, diastolic mitral annular velocities measured by tissue Doppler proved to be unaffected by the volume loss obtained in this study, and systolic velocities behavior suggested improved LV contractile function after the procedure. When evaluating the Tei index’s absolute value in a patient on maintenance HD in order to estimate global myocardial performance, one should interpret it with care, correlating it temporally with the dialysis session. Regardless of its sensitivity to preload, its prognostic value needs to be tested in this group of patients, considering its high predictive accuracy of mortality in other clinical scenarios.

**Potential Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

**REFERENCES**


