Preload Dependency of the Time Interval Between the Onset of Mitral Inflow and the Early Diastolic Annular Motion

A Hemodialysis-Related Preload Reduction Study

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Background  The novel parameter Te-E', which is the time interval between the onset of the early diastolic mitral inflow velocity (E) and the early diastolic mitral annular velocity (E'), is reported to be related to the constant of the left ventricular (LV) relaxation, and Te-E' is also reported to be useful for predicting the LV filling pressure. Methods and Results  To investigate the effect of preload reduction via hemodialysis on Te-E', 28 pairs of echocardiographic evaluations were performed just before and immediately after hemodialysis, including the measurement of the Te-E' as well as measurement of the conventional echocardiographic parameters. The baseline Te-E' was 17.9±28.1 ms, which correlated with the ratio of E/E' (r=0.49, p=0.008). After hemodialysis, Te-E' was shortened to −3.2±34.1 ms, which was a significant change from baseline (p=0.001).

Conclusions  As Te-E' is a preload dependent parameter, the intravascular volume status should be taken into account when the clinical application of Te-E' is considered as an index of LV relaxation. (Circ J 2007; 71: 669–674)

Key Words: Cardiac function; Diastole; Doppler Pulsed Echocardiography; Ultrafiltration
mitral E wave deceleration time and the IVRT. The mitral annular velocity parameters at the lateral and medial mitral annulus were also obtained on the apical 4-chamber view. The peak E’ velocity and late peak diastolic annular velocity (A’) of each annulus were measured (ie, E’med, A’med, E’lat and the A’lat. E’mean and A’mean were calculated as the average of the velocity parameters measured at the lateral and medial annulus). Each of the conventional and tissue Doppler parameters was measured for 3 consecutive beats and then averaged.

Diastolic function was assessed using pulsed-wave Doppler examination of the mitral and pulmonary venous inflow, TDI of the mitral annular velocities, and the LAVi as previously described,11 and was classified as normal, impaired relaxation with normal or near normal filling pressures (grade I), impaired relaxation with moderate elevation of the filling pressures (grade II, “pseudonormal filling”), and impaired relaxation with marked elevation of the filling pressures (grade III, “restrictive filling”).11–14

Measurement of Time Intervals

The recordings were stored digitally, and analysis was done by an investigator who was unaware of the clinical status of the patients. For the calculation of TE-E’, the time interval s were measured between the peak of the R wave and the onset of early diastolic mitral inflow and early diastolic mitral annular motion before (A) and after (B) hemodialysis (HD). Note that before HD, the mitral inflow (dashed line) begins earlier than the mitral annular motion, whereas the annular movement begins slightly earlier than the mitral inflow after HD.

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Corrected TR-E = \( \frac{TR-E}{RR_{E}} \)

Corrected TR-E’ = \( \frac{TR-E’}{RR_{E’}} \)

Corrected TE-E’ = \( \frac{TR-E - TR-E’}{RR_{E}} \)

where RR_{E} and RR_{E’} mean the RR interval during the measurement of E’ and E, respectively.15–17

Statistical Analysis

Statistical analysis was performed using the statistical package SPSS 11.5 (SPSS Interactive Graphics, Version 11.50, SPSS Inc, Chicago, IL, USA). The data are presented as means±SD or frequencies. For the analysis of changes in the LAVi, the conventional Doppler parameters, the TDI parameters and the time interval parameters, the variables measured before HD were compared by paired t-test with those measured after HD. If the data did not have a normal distribution, then the Wilcoxon signed-rank test was used. The 2-tailed Pearson’s method or Spearman’s correlation analysis was used to evaluate the correlation between the conventional Doppler parameters and the time interval parameters according to the results of the normality tests. To evaluate the intra- and interpersonal measurement variability, the measurements were performed off-line in 9 randomly selected cases by 2 investigators who were unaware of the status of the patients. The intraclass coefficient for reliability test was 0.906 (n=9, p<0.001) before HD, and 0.783 (n=9, p=0.005) after HD, respectively. A p-value of <0.05 was considered statistically significant.

Results

Baseline Characteristics of the Study Population (Table 1)

Among the 28 examinations, 15 were done on men. The mean LVEF of the patients was 61.6±8.2%, and 7 patients had an enlarged LV end-diastolic dimension (LVEDD

Table 1  Baseline Characteristics and Echocardiographic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean±SD or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55±13.1</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>15 (53.6%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.3±8.5</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.63±0.16</td>
</tr>
<tr>
<td>LA volume index (ml/m²)</td>
<td>38.4±13.4</td>
</tr>
<tr>
<td>Ultrafiltration volume (L)</td>
<td>68.6±7.1</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>61.6±8.2</td>
</tr>
<tr>
<td>LV hypertrophy</td>
<td>11 (39.3%)</td>
</tr>
<tr>
<td>LV dilation</td>
<td>7 (25.0%)</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>5 (17.9%)</td>
</tr>
<tr>
<td>Diastolic dysfunction grade</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>3 (10.7%)</td>
</tr>
<tr>
<td>Grade I</td>
<td>14 (50.0%)</td>
</tr>
<tr>
<td>Grade II</td>
<td>10 (35.7%)</td>
</tr>
<tr>
<td>Grade III</td>
<td>1 (3.6%)</td>
</tr>
</tbody>
</table>

n=28.

BSA, body surface area; LA, left atrium; LVEF, left ventricle ejection fraction; LV, left ventricle.
>57 mm). LV wall thickness >11 mm was found in 11 patients. The mean LAVi was 38.4±13.4 ml/m<sup>2</sup> and 17 patients (60.7%) had a LAVi >32 ml/m<sup>2</sup>. There were 11 patients (39.3%) with diastolic dysfunction grade II or III, and only 3 patients (10.7%) had normal diastolic function. Five patients had pericardial effusion, but the amount was minimal to small (<1 cm in depth).

**Effect of HD on Clinical Parameters and Cardiac Dimensions (Table 2)**

Baseline body weight was 61.3±8.5 kg and was significantly decreased to 58.5±8.2 kg by HD (p<0.001). Systolic blood pressure was decreased and heart rate increased significantly (p=0.039 and p=0.003, respectively). LVEDD and LV end-systolic dimension were significantly decreased by HD (p=0.006 and p=0.018, respectively), but LVEF was unchanged (p=0.407). The LA volume also decreased significantly by HD (38.4±13.4 ml/m<sup>2</sup> to 28.8±12.6 ml/m<sup>2</sup>, p<0.001).

**Changes in the Conventional Doppler and TDI Parameters After HD**

The baseline conventional Doppler and TDI parameters and the changes in these parameters after HD are shown in Table 3. Before HD, the mean E velocity was 84.9±27.2 cm/s and the mean A velocity was 89.3±22.1 cm/s. The E/A was 9.9±3.9, and an E/A >15 was observed in 11 patients (39.3%), which suggested an elevated LV diastolic filling pressure. After HD, the E velocity was decreased from 84.9±27.2 cm/s to 63.3±27.5 cm/s (p<0.001). The E/A was also decreased by 0.8±1.3 cm/s (p=0.002) and 0.6±1.5 cm/s (p=0.040) respectively. The IVRT was significantly increased from 107.3±17.6 ms to 112.2±15.6 ms (p=0.026). The E/E’mean was significantly reduced (13.6±4.7 to 11.1±3.8, p<0.001), and it was higher than 15 in only 4 patients after HD.

**Effect of HD on the Time Interval Parameters (Table 4)**

Before HD, the mean T<sub>E-E'</sub> was 18.3±26.1 ms, which was...
### Table 4 Change in the Time Interval Parameters by HD

<table>
<thead>
<tr>
<th>Time interval parameters (ms)</th>
<th>Before HD</th>
<th>After HD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td></td>
</tr>
<tr>
<td>TR-E</td>
<td>450.9±31.5</td>
<td>427.8±35.9</td>
<td>0.002</td>
</tr>
<tr>
<td>TR-E (septal)</td>
<td>468.6±37.0</td>
<td>424.7±62.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TR-E (lateral)</td>
<td>469.9±56.7</td>
<td>426.2±54.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TR-E (mean)</td>
<td>469.3±44.5</td>
<td>425.5±56.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TE-E (septal)</td>
<td>17.7±22.2</td>
<td>–3.1±38.6</td>
<td>0.009*</td>
</tr>
<tr>
<td>TE-E (lateral)</td>
<td>19.0±38.5</td>
<td>–1.6±31.9</td>
<td>0.005</td>
</tr>
<tr>
<td>TE-E (mean)</td>
<td>18.3±26.1</td>
<td>–2.3±31.2</td>
<td>0.002*</td>
</tr>
<tr>
<td>Corrected TR-E</td>
<td>484.7±28.9</td>
<td>471.4±33.1</td>
<td>0.019</td>
</tr>
<tr>
<td>Corrected TR-E (septal)</td>
<td>502.7±30.0</td>
<td>467.3±52.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Corrected TR-E (lateral)</td>
<td>502.6±46.8</td>
<td>469.1±44.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Corrected TR-E (mean)</td>
<td>502.7±34.2</td>
<td>468.2±44.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Corrected TE-E (septal)</td>
<td>18.0±26.5</td>
<td>–4.1±41.7</td>
<td>0.005</td>
</tr>
<tr>
<td>Corrected TE-E (lateral)</td>
<td>17.9±40.2</td>
<td>–2.2±36.0</td>
<td>0.006</td>
</tr>
<tr>
<td>Corrected TE-E (mean)</td>
<td>17.9±28.1</td>
<td>–3.2±34.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

n=28.

The paired t-test was used for comparison of the parameters before and after HD, *Wilcoxon signed rank test used.

TR-E, time interval between peak R and the onset of E velocity; TR-E’, time interval between peak R and the onset of E’ velocity; TE-E’, time interval between onset of E and E’ velocity.

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**Fig 2.** Correlations between the time interval parameters and the ratio of the early diastolic peak mitral inflow velocities and the early diastolic peak mitral annular velocities. (Left panel A) Correlation between the corrected TE-E’ and E/E’mean as analyzed with Pearson’s 2-tailed method. (Right panel B) Correlation between the changes of the corrected TE-E’ and the changes of E/E’mean.

**Fig 3.** Correlations between the TE-E’ and the E/E’ according to the grade of diastolic dysfunction. (Left panel A) Relationship between the TE-E’ and E/E’ in patients whose diastolic dysfunction grades (DG) are normal (DG 0) or grade I, analyzed by Spearman’s correlation. (Right panel B) Same analysis in patients whose diastolic DG is II or III.
the simple difference between TR-E and TR-E. After correction for the measured RR interval according to the formulae 1–3, the mean corrected TR-E was 17.9 ± 28.1 ms. After HD, the TR-E and corrected TR-E were measured as –2.3 ± 31.2 ms and –3.2 ± 34.1 ms respectively; these values were reduced from baseline by 20.6 ± 28.9 ms and 21.1 ± 29.3 ms, respectively (p = 0.002 and p = 0.001, respectively).

**Correlation Between the Doppler and Time Interval Parameters**

The corrected TR-E and E/E’, which were measured before HD, showed an intermediate level of correlation by Pearson’s correlation analysis (r = 0.49, p = 0.008). The changes in the corrected TR-E and E/E’ after HD, ΔTR-E and ΔE/E’, also showed an intermediate level of correlation (r = 0.41, p = 0.031, Fig 2).

Subgroup analysis of the relationship between TR-E and E/E’ in 11 patients with grade II or III diastolic dysfunction showed a strong correlation according to Spearman’s correlation analysis (r = 0.80, p = 0.003), whereas the correlation between TR-E and E/E’ in 17 patients with normal or grade I diastolic dysfunction was statistically insignificant (r = 0.40, p = 0.12, Fig 3). This might be related to the CO (LAVI), and TE-E’ might be more influenced by LV relaxation itself rather than E/E’.

**Preload Dependency of TE-E’**

The time sequence of E-E’ was even reversed in some patients after preload reduction with HD. Our hypothesis was that acute reduction of preload, which is related to the mean LA pressure, would delay the crossover point of the LA–LV pressure curve, and thus would shorten the TE-E’. However, that was not clearly demonstrated in this study, because TE-E’ was not prolonged but rather shortened after HD (Table 4). Nevertheless, relatively greater shortening of TR-E than TR-E resulted in a reduction of TE-E by HD, which suggests that with reduced LA pressure, the early diastolic LV suction might have a more important role in the development of early diastolic mitral inflow. Therefore, TE-E’ would not be free from the effect of preload. Although there is 1 study that is not consistent with our results, most other previous studies regarding TE-E’ support our result that TE-E’ is related to LV filling pressure, which means LV end-diastolic pressure (LVEDP).1,2 The effect of preload reduction with ultrafiltration is explained very well in this regard. However, for confirmation of our results, further investigation with different load-challenging methods and a larger number of study subjects are needed.

**Study Limitations**

The sample size was relatively small for the subgroup analysis; repeated tests were done in 7 patients and we considered each examination as an independent case. However, the interval between the repeated examinations was more than 6 months. Second, we could not evaluate either LVEDP or CO because of the invasiveness of the measurement procedure. As an index of preload, LAVI and LV dimensions could provide indirect evidence of loading conditions. However, measurement of CO would have provided more invaluable information about diastolic function before and after HD. We did not evaluate the TDI’s at all 4 anular segments for the measurement of TE-E but rather those at the septal and lateral annular movement were evaluated. However, because patients with regional wall motion abnormality were excluded from our study, we assumed that these velocities were sufficient for evaluating TE-E. Moreover,
additional measurements at the anterior and posterior annulus would result in difficulties in choosing a similar RR interval for the measurement of TE-E'. As measuring the time intervals of TR-E and TR-E' in same cardiac length was impossible, we measured them with a difference in the RR interval of less than 50 ms. In a previous study, TR-E and TR-E' were evaluated in cardiac cycles with an RR interval difference of less than 5 ms; but it was impossible in our study to obtain the images of the different cardiac cycles of a similar RR interval with a difference less than 5 ms, so adjustment of TE-E' with each measured RR interval was performed as described next. Although our results for load dependency were similar, irrespective of the correction for the RR interval difference, future studies concerning the time interval should be performed with simultaneous measurement of the conventional Doppler and tissue Doppler parameters to overcome this limitation.

Clinical Implications

TE-E' could be influenced by acute change in filling pressure, especially in patients with more severely impaired diastolic function. Therefore, as it is a preload dependent parameter, loading conditions should be taken into account when considering its clinical application.

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References