Myocardial performance (Tei) index is normal in diastolic and systolic heart failure induced by pressure overload in rats

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Received 31 March 2010; accepted after revision 20 May 2010; online publish-ahead-of-print 18 June 2010

Aims
Myocardial performance index (MPI), or Tei index, is a Doppler echocardiographic parameter defined as the sum of the isovolumic contraction and relaxation times divided by the ejection time. It is considered a reliable parameter for global left ventricular function. However, the interpretation of this index is not fully clear in diastolic dysfunction. We measured MPI in a pressure-overload model of rats with severe diastolic with or without systolic dysfunction and examined its usefulness as a parameter for cardiac function in a hypertensive heart failure model.

Methods and results
Pressure overload was created by placement of a metal clip around the thoracic aorta [transverse aortic constriction (TAC)] at a weight of 40–50 g. Transthoracic echocardiography including Doppler analysis and invasive left ventricular catheter examination were performed 10 and 20 weeks after TAC (n = 6 for each time point). While left ventricular ejection fraction was over 50% in all TAC animals after 10 weeks (56.3 ± 2.3%), it was below 50% in all TAC animals after 20 weeks (45.4 ± 1.0%). E/E′ was significantly larger in the TAC groups at both time points and the time constant τ by Millar catheter was also elevated in the TAC groups. On the other hand, MPI was not different compared with the control groups (10 weeks: 0.47 ± 0.09 vs. 0.44 ± 0.04; 20 weeks: 0.38 ± 0.03 vs. 0.46 ± 0.07).

Conclusion
MPI is not a reliable parameter for the assessment of contractile function in pressure-overload heart failure. It is normal in diastolic dysfunction with or without preserved ejection fraction.

Keywords
Myocardial performance index • Pressure overload • Heart failure

Introduction
Systolic and diastolic functions influence each other in concert to generate cardiac output. They can be assessed separately using echocardiographic parameters such as the ejection fraction or fractional shortening for systolic function and the quantification of mitral waves (E and A) for diastolic function. Thus far, the classical distinction between diastolic and systolic contractile dysfunction is made, although the validity of this practice has been questioned. Therefore, several attempts have been made to develop parameters assessing contractile function as a whole, considering both the systolic and diastolic components at the same time.

The myocardial performance index (MPI), or Tei index, is a Doppler echocardiographic parameter and defined as the sum of the isovolumic contraction and relaxation times (ICT and IRT) divided by the ejection time (ET). MPI has been demonstrated to be a reliable and reproducible parameter for the evaluation of left ventricular systolic and diastolic dysfunction in many kinds of heart disease in human. Furthermore, a number of studies have documented that MPI is independent of heart rate, arterial pressure, and preload. However, the value of MPI in diastolic dysfunction is not yet fully clear and the evaluation of its value in animals has been mainly limited to spontaneously hypertensive rats. The purpose of this study was to determine MPI in a model of pressure-overload-induced heart failure in rats displaying diastolic dysfunction with or without systolic dysfunction and to examine its usefulness as a parameter for cardiac function.

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Methods

Animal model and study protocol
Male Sprague Dawley rats were obtained from Charles River (Sulzfeld, Germany). The use of animals was consistent with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH publication No. 85-23, revised 1996) and the experimental protocols were approved by the local Animal Welfare Committee of the University of Leipzig, Germany. The model of hypertrophy and heart failure has been described in detail before.11 Pressure overload was created by placement of a metal clip with a remaining opening of 0.35 mm around the aortic arch between the brachiocephalic trunk and the left carotid artery [transverse aortic constriction (TAC)] at a weight of 40–50 g. As we previously reported,12 the animals show systolic dysfunction with pleural effusion and dyspnoea 18–20 weeks after TAC. For the examination in diastolic dysfunction both with preserved and reduced ejection fraction, the animals were analysed at 10 and 20 weeks after TAC (n = 6 for each time point). The data were compared with age-matched control groups (n = 4 for each time point).

Echocardiographic examination
The animals were anesthetized with fentanyl, midazolamhydrochlorid, and medetomidinhydrochlorid (0.005, 2, and 0.15 mg/kg). Chests were shaved and the rats were examined in supine position by a Sonos 5500 ultrasound system (Philips Medical Systems, Andover, MA, USA) with a 12 MHz phased array transducer. Two-dimensional short-axis views of the left ventricle at the papillary muscle level were obtained. Two-dimensional guided M-mode tracings were recorded with a sweep speed of 150 mm/s. The following parameters were measured: heart rate, left ventricular end-diastolic and systolic dimension, interventricular septal thickness in diastole, and left ventricular posterior wall thickness in diastole. Based on these measurements, fractional shortening13 and left ventricular mass index16 were obtained. Left ventricular ejection fraction (LVEF) was evaluated by modified Simpson's rule.

The pulsed Doppler of the left ventricular inflow (E and A waves) was assessed in the apical four-chamber view, and the sample volume was placed at the mitral tip level. Pulse-wave tissue Doppler was obtained from the four-chamber view, and the sample volume was placed on the basal interventricular septum. The early and late diastolic waves (E' and A') and the systolic wave (S') were detected and their peak velocities were measured. Furthermore, E/E' was also calculated as an index of preload. Cardiac output was calculated as (stroke volume) × (heart rate) and cardiac index was defined as the ratio of cardiac output to body weight (mL/min/g).14

MPI, defined as the sum of the ICT and IRT divided by the ET, was obtained from Doppler recordings of left ventricular inflow and outflow.15 The index was derived as (a − b)/b, where 'a' is the interval between the cessation and the onset of the mitral inflow, and 'b' is the ET of the left ventricular outflow. These values were corrected for heart rate: ICT-c = ICT/RR, where ICT is expressed in milliseconds and RR in seconds.15 Figure 1 shows the representative images of Doppler measurement for the determination of MPI at baseline and 20 weeks after TAC. The reproducibility of the measurement was obtained by measuring MPI in 10 separate animals of pressure overload three times per animal. The coefficient of variation (standard deviation divided by mean value) in those three-fold measurements was between 1.6 and 14.6% (mean 8.2%) representing adequate precision.

Invasive assessment of cardiac function
Invasive pressure measurement using a 2 F Millar catheter was performed as described before.16 The dp/dt max and min was indexed by dividing by left ventricular systolic pressure. τ, the time constant of isovolumic left ventricular pressure decline, was calculated offline according to the method reported by Weiss et al.17

Statistical analysis
Data are presented as mean ± SEM. Data were analysed using a Student’s t-test for intergroup comparison (two groups). If more

| Table 1 | Body, lung, and atrial weights of rats after 10 and 20 weeks of pressure overload and control |
|---------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
|         | Control (n = 4)                                 | TAC (n = 6)                                     | Control (n = 4)                                 | TAC (n = 6)                                     |                                                  |                                                  |                                                  |
| Body weight (g) | 359 ± 8                                      | 372 ± 30                                      | 408 ± 8**                                      | 439 ± 25                                       |                                                  |                                                  |                                                  |
| Lung weight (mg) | 1360 ± 12                                     | 3910 ± 330*                                   | 1664 ± 30*                                     | 4149 ± 389*                                    |                                                  |                                                  |                                                  |
| LW/BW   | 6.3 ± 0.2                                      | 12.0 ± 1.1*                                   | 3.8 ± 0.1                                      | 10.0 ± 1.0*                                    |                                                  |                                                  |                                                  |
| Atrial weight (mg) | 109 ± 10                                      | 326 ± 33**                                    | 156 ± 25                                       | 537 ± 58**                                     |                                                  |                                                  |                                                  |

Data are mean ± SEM. LW/BW, lung weight/body weight; TAC, transverse aortic constriction.

*P < 0.05.

**P < 0.01 compared with age-matched controls.

##P < 0.005.

###P < 0.01 compared with 10 weeks.
than two groups were compared, a one-way analysis of variance with post hoc comparisons using Tukey’s test was applied. Differences among groups were considered statistically significant if \( P < 0.05 \).

### Results

Table 1 shows the body, lung, and atrial weights of rats after 10 and 20 weeks of pressure overload and age-matched control. Although there was no significant difference between the groups in body weight, lung and atrial weights were significantly larger in the TAC groups both after 10 and 20 weeks, which indicates decreased active relaxation due to pressure overload.

Table 2 shows the invasive catheter data. Left ventricular systolic pressure was significantly higher in the TAC groups. \( \tau \) was significantly increased in the TAC groups both after 10 and 20 weeks, which indicates decreased active relaxation due to pressure overload.

### Table 2: Systolic and diastolic parameters by Millar catheter analysis

<table>
<thead>
<tr>
<th></th>
<th>10 weeks Control (n = 4)</th>
<th>10 weeks TAC (n = 6)</th>
<th>20 weeks Control (n = 4)</th>
<th>20 weeks TAC (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left ventricular pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
<td>108 ± 6</td>
<td>184 ± 13***</td>
<td>85 ± 4*</td>
<td>298 ± 58*</td>
</tr>
<tr>
<td>End-diastolic (mmHg)</td>
<td>6 ± 1</td>
<td>16 ± 5</td>
<td>5 ± 2</td>
<td>26 ± 5***</td>
</tr>
<tr>
<td>dp/dt max (index)</td>
<td>37 ± 1</td>
<td>19 ± 2***</td>
<td>41 ± 2</td>
<td>17 ± 1**</td>
</tr>
<tr>
<td>dp/dt min (index)</td>
<td>26 ± 1</td>
<td>19 ± 1**</td>
<td>24 ± 4</td>
<td>18 ± 0</td>
</tr>
<tr>
<td>( \tau ) (ms)</td>
<td>18 ± 1</td>
<td>23 ± 2*</td>
<td>15 ± 1</td>
<td>23 ± 1**</td>
</tr>
</tbody>
</table>

Data are mean ± SEM. TAC, transverse aortic constriction.

*\( P < 0.05 \).

**\( P < 0.01 \) compared with age-matched controls.

***\( P < 0.05 \) compared with 10 weeks.

### Table 3: Basic echocardiographic parameters and Doppler data

<table>
<thead>
<tr>
<th></th>
<th>10 weeks Control (n = 4)</th>
<th>10 weeks TAC (n = 6)</th>
<th>20 weeks Control (n = 4)</th>
<th>20 weeks TAC (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate (bpm)</strong></td>
<td>297 ± 8</td>
<td>286 ± 17</td>
<td>273 ± 10</td>
<td>277 ± 8</td>
</tr>
<tr>
<td>LVDd (mm)</td>
<td>7.4 ± 0.4</td>
<td>8.7 ± 0.4</td>
<td>8.4 ± 0.3</td>
<td>9.3 ± 0.4</td>
</tr>
<tr>
<td>LVDs (mm)</td>
<td>4.6 ± 0.4</td>
<td>5.7 ± 0.5</td>
<td>5.1 ± 0.3</td>
<td>6.9 ± 0.3**</td>
</tr>
<tr>
<td>%FS (%)</td>
<td>37.8 ± 3.3</td>
<td>35.7 ± 3.2</td>
<td>39.6 ± 1.1</td>
<td>25.2 ± 1.5**</td>
</tr>
<tr>
<td>LVEF (Simpson) (%)</td>
<td>64.1 ± 0.7</td>
<td>56.3 ± 2.3</td>
<td>56.0 ± 2.5*</td>
<td>45.4 ± 1.0**##</td>
</tr>
<tr>
<td>LVMI (g/kg)</td>
<td>1.9 ± 0.1</td>
<td>2.7 ± 0.2**</td>
<td>1.9 ± 0.1</td>
<td>2.5 ± 0.2</td>
</tr>
<tr>
<td>IVST (mm)</td>
<td>2.1 ± 0.1</td>
<td>2.6 ± 0.1*</td>
<td>1.7 ± 0.0*</td>
<td>2.4 ± 0.2</td>
</tr>
<tr>
<td>LVMI (g/kg)</td>
<td>3.0 ± 0.1</td>
<td>6.0 ± 0.6**</td>
<td>2.9 ± 0.0</td>
<td>4.8 ± 0.3**</td>
</tr>
<tr>
<td><strong>Transmitral Doppler</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E (cm/s)</td>
<td>75.2 ± 3.1</td>
<td>105.2 ± 5.9**</td>
<td>70.6 ± 2.3</td>
<td>112.9 ± 8.9*</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>56.8 ± 2.9</td>
<td>29.6 ± 7.0*</td>
<td>43.9 ± 5.5</td>
<td>26.2 ± 3.1*</td>
</tr>
<tr>
<td>E/A</td>
<td>1.3 ± 0.1</td>
<td>4.7 ± 1.0</td>
<td>1.7 ± 0.2</td>
<td>4.8 ± 0.8*</td>
</tr>
<tr>
<td><strong>Diastolic time</strong></td>
<td>67.0 ± 6.0</td>
<td>47.1 ± 4.0*</td>
<td>68.3 ± 7.0</td>
<td>38.5 ± 2.5**</td>
</tr>
<tr>
<td><strong>Tissue Doppler</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E’ (cm/s)</td>
<td>9.0 ± 0.6</td>
<td>5.7 ± 0.4**</td>
<td>8.6 ± 0.7</td>
<td>6.1 ± 0.4**</td>
</tr>
<tr>
<td>A’ (cm/s)</td>
<td>7.3 ± 0.4</td>
<td>5.8 ± 0.7</td>
<td>6.8 ± 1.1</td>
<td>6.7 ± 0.4</td>
</tr>
<tr>
<td>S’ (cm/s)</td>
<td>6.9 ± 0.3</td>
<td>5.3 ± 0.4*</td>
<td>6.7 ± 0.4</td>
<td>6.0 ± 0.5</td>
</tr>
<tr>
<td>E/A’</td>
<td>1.2 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>1.3 ± 0.1</td>
<td>0.9 ± 0.0**</td>
</tr>
<tr>
<td>E/E’</td>
<td>12.0 ± 0.6</td>
<td>19.4 ± 2.4*</td>
<td>8.3 ± 0.7**</td>
<td>19.2 ± 2.4*</td>
</tr>
</tbody>
</table>

Data are mean ± SEM. DTc, deceleration time; FS, fractional shortening; IVST, interventricular septal thickness; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVMI, left ventricular posterior wall thickness; TAC, transverse aortic constriction.

*\( P < 0.05 \).

**\( P < 0.01 \) compared with age-matched controls.

***\( P < 0.05 \) compared with 10 weeks.

****\( P < 0.01 \) compared with 10 weeks.

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Table 3 shows the basic echocardiographic parameters and Doppler data. Although the difference in the left ventricular chamber size was minimal, LVEF was significantly reduced in the TAC groups both after 10 and 20 weeks. While LVEF was over 50% in all TAC animals after 10 weeks (56.3 ± 2.3%), it was below 50% in all TAC animals after 20 weeks (45.4 ± 1.0%). Transmitral E wave was significantly larger and A wave and deceleration time were significantly smaller in the TAC groups compared with the control. E/E’ was significantly larger in the TAC groups both after 10 and 20 weeks. Thus, the TAC animals had severe diastolic dysfunction with preserved ejection fraction (>50%) after 10 weeks and severe diastolic dysfunction with reduced ejection fraction (<50%) after 20 weeks.

Table 4 and Figure 2 show the values of MPI and cardiac index. While cardiac index was still normal after 10 weeks, it was significantly reduced after 20 weeks. In contrast, MPI was not different compared with the control groups both after 10 and 20 weeks (0.47 ± 0.09 vs. 0.44 ± 0.04 and 0.38 ± 0.03 vs. 0.46 ± 0.07, respectively). Both of the corrected isovolumic contraction time (ICT-c) and corrected ejection time (ET-c) were significantly increased after 20 weeks. There was no significant correlation between MPI and cardiac index.

### Discussion

We show here that in a pressure-overload model, MPI is normal in diastolic dysfunction both with preserved and reduced LVEF. These results suggest caution for using MPI in animal models of pressure overload. These findings require further discussion.

While many clinical studies and experimental studies had documented usefulness of this index, the diastolic dysfunction in these studies are rather mild. One considerable problem is its normalization in severe diastolic dysfunction. Although we did not intend to compare animals with humans, our results underscore such potentially significant limitations. We show that MPI is normal in diastolic dysfunction both with preserved and reduced LVEF in a pressure-overload model. Our findings may represent a significant drawback for the usefulness of this parameter to assess global myocardial performance. Our study finds support from the clinical arena. Sud and Massel reported a study examining MPI in different degrees of aortic valve stenosis in human. In their study, MPI was normal in patients with severe aortic valve stenosis and LVEF < 40%, and they already suggested the limitation of this index. Lindqvist et al. recently reported normal MPI in patients with aortic valve stenosis and normal LVEF both before and after operation.
Our investigation does not allow the comparison of the clinical scenario because the model is not fully representative of the clinical picture of patients with chronic pressure overload. For example, the degree of systolic dysfunction in our model is rather moderate compared with at times substantially impaired ejection fraction in patients. However, the lack of severe systolic dysfunction in our rats may be a species-specific phenomenon because these rats develop severe symptoms of heart failure and die a long time before they ever reach an ejection fraction of 30%. Another limitation may be the small sample size of only four to six animals per group. Nonetheless, since the message is based on the absence of major MPI difference between the groups and the values are almost identical, it is unlikely that an increase in sample size will significantly change the results.

Although those limitations have to be accepted, the reason for a normal MPI at times when there is significant contractile dysfunction (either diastolic or systolic or both) is not easily understood. The reason for a normal MPI has been attributed to the biphasic nature of IRT (prolonged in abnormal relaxation and normalized in further diastolic dysfunction). The IRT in our model was also a little shorter but still in normal range. Furthermore, the loading conditions such as afterload and preload elevations can prolong ICT and ET, respectively. We showed the higher loading conditions such as afterload and preload elevations can also a little shorter but still in normal range. Furthermore, the reason for a normal MPI at times when there is significant contractile dysfunction (either diastolic or systolic or both) is not easily understood.

We therefore conclude that the MPI is not a reliable parameter for the assessment of contractile function in our rat model of pressure-overload heart failure and should be used with caution in general in situation where changes in afterload are present.

Acknowledgements

Y.S. is a recipient of a research fellowship from the Uehara memorial foundation in Japan.

Funding

T.D. is Heisenberg-Professor of the Deutsche Forschungsgemeinschaft (DFG) at the University of Leipzig and supported by grants from the DFG (DO 602/4-1, 6-1, 8-1 and 9-1).

Conflict of interest: none declared.

References

10. Salemi VM, Pires MD, Cestari IN, Cestari IA, Picard MH, Lehrner AA et al. Echocardiographic assessment of global ventricular function using the myocardial performance index in rats with pressure-overload heart failure and should be used with caution for the assessment of contractile function in our rat model of pressure-overload heart failure. For the assessment of contractile function in our rat model of pressure-overload heart failure and should be used with caution for the assessment of contractile function in our rat model of pressure-overload heart failure.