Preclinical research

The effects of changes in loading conditions and modulation of inotropic state on the myocardial performance index: comparison with conductance catheter measurements

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Aim The myocardial performance index (MPI), or Tei index, has been shown to be useful in the assessment of global myocardial performance. There are few invasive data however, which examine its load dependence or sensitivity to acute changes in contractile function. The purpose of this study was therefore to study formally the effect of clinically relevant changes in these parameters in an animal model.

Methods and results We examined 10 Yorkshire pigs using echocardiographic assessment and simultaneous measurements of intraventricular pressure and volume by conductance catheterization. With dobutamine infusion, there was no significant change in the MPI (0.26 ± 0.13–0.22 ± 0.11; \( p = 0.42 \)), but \( \frac{dP}{dt}_{\text{max}} \) increased significantly (1001 ± 240–1569 ± 532 mm Hg/s, \( p < 0.001 \)). Afterload increase (40% change in ventricular pressure) and preload reduction (20% change in ventricular volume) were associated with significant increases in the MPI (0.26 ± 0.13–0.49 ± 0.20; \( p < 0.005 \) and 0.26 ± 0.13–0.51 ± 0.20; \( p < 0.001 \), respectively) without any significant change in maximal elastance (Ees).

Conclusions The MPI, or Tei index, is significantly affected by acute changes in loading conditions but is unable to consistently detect acute changes in contractile function.

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KEYWORDS
Ventricle;
Contractility;
Echocardiography

Introduction

The ideal index of ventricular performance should be sensitive to contractile change, independent of loading conditions, easily obtained and reproducible.\(^1\) Proposed in 1995 as a non-invasive index of ventricular contractility, derived from echocardiographic Doppler flow measurements, the Tei index or myocardial performance index (MPI)\(^2\) has been shown to be useful in the assessment of global myocardial performance. Indeed, it has been shown to be a useful prognostic indicator in patients with dilated cardiomyopathy of varying aetiology,\(^3\)–\(^5\) chronic pulmonary disease,\(^6\) and

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amyloidosis, and has been proposed as an index of function in foetal cardiac assessment. Recently however, the MPI has been shown to have limitations in patients with severe impairment of right ventricular function caused by myocardial infarction. While the MPI has been shown to be significantly correlated with invasive measurements of left ventricular dp/dt_{max} in humans, and also left ventricular end-diastolic pressure and ejection fraction, it remains uncertain whether this index is simply a surrogate phenomenon, or whether it has direct functional relevance. Furthermore, there are few invasive data examining its load dependence, or sensitivity to acute changes in contractile function.

The purpose of this study was therefore to study formally the effect of clinically relevant changes in left ventricular loading conditions and inotropy on the MPI.

Methods

We studied 10 Yorkshire pigs ranging from 5 to 19 kg. The study conformed to the guidelines of the American Heart Association on research animal experiments. Our experimental preparation has previously been described in detail. Briefly, animals were pre-medicated with midazolam 0.3 mg/kg and acepromazine 3 mg/kg prior to endotracheal intubation and ventilated with a Ventimenter® Controller II (Air-Shields, Pennsylvania, USA) ventilator. Anaesthesia was maintained with isoflurane 2% in a mixture of N_2O and oxygen. Muscle relaxation was maintained by intravenous pancuronium infusion (0.8 μg/kg/min). Arterial blood gases were sampled to ensure adequate oxygenation and ventilation throughout the study.

Heart rate was controlled by right atrial pacing using a 5F endocardial pacing catheter inserted via the left external jugular vein and connected to an external pulse generator (Medtronic 5388, Medtronic Minneapolis, USA). The right atrium was paced at a constant basal rate of 140 bpm at all stages. Via the right carotid artery, a custom-made 8 polar 5F combination conductance-pressure catheter (Millar Instruments, Houston, USA) was placed into the apex of the LV under fluoroscopic guidance. The micromanometer pressure transducer output was fed to a custom-built amplifier. The conductance catheter was connected to a signal-processing unit (Sigma 5DF, Cardodynamics Corp, Leiden, Netherlands). A 5F Miller balloon septostomy catheter (Edwards Lifesciences, USA) was placed via the right external jugular vein at the junction of the inferior vena cava and the right atrium, and subsequently inflated to reduce preload in order to generate a series of pressure–volume loops. Via the left carotid artery, a 7F balloon catheter (Meditech, Watertown, MA) was placed in the ascending aorta and prepared for inflation to modify LV afterload. Via the right external jugular vein, a standard 5F thermodilution catheter (Baxter Healthcare, Dearfield, IL), connected to a dedicated cardiac output processing computer (Com2, Baxter, Edwards, Dearfield, IL), was placed in the main pulmonary artery. Pressure and volume data were digitized at 1000 Hz, and stored on a personal computer with dedicated software for later analysis. In order to calibrate the conductance volume signal, parallel conductance was calculated following injection of 2 ml of 10% NaCl into the main pulmonary artery, and the gain constant a was calculated as the ratio of conductance-derived stroke volume and the stroke volume measured by thermodilution.

Echocardiography

Transthoracic echocardiographic measurements were made using a Vivid 7 echo machine (GE Vingmed) with simultaneous electrocardiographic monitoring. Measurements of Doppler inflow across the mitral valve were made from the four-chamber view, with the sample volume positioned at the tips of the mitral valve leaflets. Aortic outflow Doppler measurements were made with the sample volume placed just below the aortic valve from an apical long axis view. Data were stored digitally and analysed off-line by a single observer (MV).

All physiological data were obtained during apnoea to minimise cardiopulmonary interactions. Echocardiography and pressure–volume data were simultaneously recorded, and cardiac output was measured at each stage.

The measurements were obtained during the following protocol, chronologically:

1. Baseline, echocardiographic measurements were made as described above. Subsequently, conductance catheter derived pressure–volume data were obtained before and during transient preload reduction by balloon occlusion of the inferior vena cava.

2. Afterload increase, by descending aortic balloon occlusion with measurements as at baseline.

3. Change in inotropy. First 1 mg/kg/min of esmolol was infused for 10 min. After a 10-min washout period, dobutamine was infused at a rate of 10 μg/kg/min for 10 min. Data were obtained as at baseline, after stabilising at each dose and also after the washout period of 10 min immediately prior to starting dobutamine.

4. Preload alteration. Preload was increased by bolus infusion of 20 ml/kg of normal saline. This was followed by preload reduction of up to 40 ml/kg of blood or up to a 20% drop in systolic blood pressure, whichever occurred first. Data as at baseline were obtained after stabilization after each intervention.

Data analysis

Pressure–volume data were analysed off-line by a single observer (MC) blinded to the data obtained by echocardiography, which were analysed by a different observer (MV). All conductance volumes were corrected for parallel conductance and the gain constant a. The maximal slope of the end-systolic (left upper shoulder) pressure–volume relation: maximal elastance (Ees) during caval occlusion, end-diastolic volume, dp/dt_{max} and dp/dt_{min}, were calculated.

The Tei index was calculated in the usual way, by the total isovolumic (contraction and relaxation) time divided by ejection time. The time from cessation of mitral valve A wave to the onset of the mitral valve E wave of the next cardiac cycle (a) is equal to the total isovolumic time (TIT) plus the ejection time (b). The Tei index was therefore calculated by the formula (a – b)/b. The average of five cardiac cycles was calculated.

Statistical analysis

Data are presented as mean ± standard deviation. Two-tailed, paired t-tests were used to compare the absolute and also the percentage changes in indices compared with baseline following modulation of contractility and alteration of loading conditions. A p-value < 0.05 was considered significant. Although this was a prospective study, as the potential magnitude of change was unknown, a power calculation was not possible.
Results

Modulation of inotropy

Data for measurements of contractile indices during modulation of inotropy by esmolol and dobutamine are summarized in Table 1. With esmolol infusion, there were no significant changes in either absolute or percentage change of any of the contractile indices as compared with baseline values.

Conversely, with dobutamine there was no significant change in the MPI (0.26 ± 0.13–0.22 ± 0.11; p = 0.42), whilst Ees and \( \frac{dP}{dt_{\text{max}}} \) increased significantly (from 2.38 ± 1.22 to 3.71 ± 2.24 mm Hg/ml; \( p = 0.04 \) and 1001 ± 240 to 1569 ± 532 mm Hg/s; \( p < 0.001 \), respectively). There was also an improvement in diastolic function from baseline as reflected by a significant change in \( \frac{dP}{dt_{\text{min}}} \) (from −1027 ± 281 to −1397 ± 338 mm Hg/s; \( p = 0.001 \)).

Analysis of changes in the components of the MPI: duration of total isovolumic time (TIT) and ejection time during modulation of inotropy with esmolol revealed a lengthening of TIT (from 47 ± 22 to 54 ± 30 ms; \( p = 0.06 \)) while there was no change in ejection time (from 183 ± 15 to 181 ± 16 ms; \( p = 0.42 \)). With dobutamine infusion, both TIT and ejection times shortened (from 47 ± 22 to 39 ± 20 ms; \( p = 0.26 \) and 183 ± 15 to 175 ± 17 ms; 0.04, respectively).

Percentage change in contractile indices, as compared with baseline values, for esmolol infusion again showed no significant changes in any of the contractile indices. With dobutamine infusion, there was no significant change in the MPI (\( p = 0.78 \)), however the percentage changes in both \( \frac{dP}{dt_{\text{max}}} \) and also Ees increased significantly (55.6 ± 27.0%; \( p = 0.0001 \) and 60.7 ± 63.5%; \( p = 0.02 \) respectively).

Changes in loading conditions

Data for measurements of contractile indices, and changes in afterload and LV end-diastolic volume are summarized in Table 2. Relative changes in the MPI with altered loading conditions are shown in Fig. 1.

With increased afterload, LV pressure increased from 71 ± 14 to 98 ± 18 mm Hg but there was no significant change in Ees from baseline (\( p = 1.0 \)). Afterload increase was, however, associated with a significant increase in the MPI (0.26 ± 0.13–0.49 ± 0.20; \( p = 0.001 \)). Whilst the percentage change in Ees from baseline was not significant (13.0 ± 39.1; \( p = 0.5 \)), there was a significant percentage change in the MPI (92.7 ± 81.8; \( p = 0.02 \)).

With preload increase, an increase in LV end-diastolic volume from 40.7 ± 13 ml to 44.2 ± 17 ml, there was no significant change in either the MPI or Ees. With preload reduction however, a change in LV volume from 40.7 ± 13 ml to 32.8 ± 11 ml, was associated with a significant increase in the MPI (0.26 ± 0.13 to 0.51 ± 0.20; \( p = 0.0005 \)) without any significant change in Ees (\( p = 0.92 \)).

Table 1 Absolute and percentage changes in contractile indices compared with baseline values during modulation of inotropy

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Esmolol (1 mg/kg/min)</th>
<th>Dobutamine (10 μg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPI</td>
<td>0.26 ± 0.13</td>
<td>0.31 ± 0.18</td>
<td>0.22 ± 0.11</td>
</tr>
<tr>
<td>Total isovolumic time (ms)</td>
<td>47 ± 22</td>
<td>54 ± 30</td>
<td>39 ± 20</td>
</tr>
<tr>
<td>Ejection time (ms)</td>
<td>183 ± 15</td>
<td>181 ± 16</td>
<td>175 ± 17</td>
</tr>
<tr>
<td>( \frac{dP}{dt_{\text{max}}} ) (mm Hg/s)</td>
<td>1001 ± 240</td>
<td>966 ± 205</td>
<td>1569 ± 532</td>
</tr>
<tr>
<td>Ees (mm Hg/ml)</td>
<td>2.38 ± 1.22</td>
<td>2.11 ± 1.10</td>
<td>3.71 ± 2.24</td>
</tr>
<tr>
<td>( \frac{dP}{dt_{\text{min}}} ) (mm Hg/s)</td>
<td>−1027 ± 2.81</td>
<td>−988 ± 251</td>
<td>−1397 ± 338</td>
</tr>
<tr>
<td>% change MPI</td>
<td>16.6 ± 27.4</td>
<td>−3.0 ± 5.8</td>
<td>55.6 ± 27.3</td>
</tr>
<tr>
<td>% change Ees</td>
<td>−14.8 ± 28.0</td>
<td>−14.8 ± 28.0</td>
<td>60.7 ± 63.5</td>
</tr>
</tbody>
</table>

*\( p < 0.05 \), ***\( p < 0.001 \) as compared with baseline value.

Table 2 Absolute and percentage changes in MPI and maximal elastance (Ees) during changes in loading conditions

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Preload increase</th>
<th>Preload reduction</th>
<th>Afterload increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic volume (ml)</td>
<td>40.7 ± 13</td>
<td>44.2 ± 17</td>
<td>32.8 ± 11</td>
<td>98 ± 18</td>
</tr>
<tr>
<td>LV systolic pressure (mm Hg)</td>
<td>71 ± 14</td>
<td>0.26 ± 0.13</td>
<td>0.24 ± 0.14</td>
<td>0.51 ± 0.20***</td>
</tr>
<tr>
<td>MPI</td>
<td>1001 ± 240</td>
<td>966 ± 205</td>
<td>1569 ± 532 ***</td>
<td>0.49 ± 0.20***</td>
</tr>
<tr>
<td>Total isovolumic time (ms)</td>
<td>47 ± 25</td>
<td>45 ± 20</td>
<td>80 ± 22***</td>
<td>81 ± 26***</td>
</tr>
<tr>
<td>Ejection time (ms)</td>
<td>183 ± 15</td>
<td>191 ± 22</td>
<td>156 ± 22***</td>
<td>165 ± 28***</td>
</tr>
<tr>
<td>Ees (mm Hg/ml)</td>
<td>2.03 ± 1.53</td>
<td>2.82 ± 1.56</td>
<td>1.76 ± 0.67</td>
<td>2.65 ± 1.00</td>
</tr>
<tr>
<td>% change MPI from baseline</td>
<td>10.6 ± 94</td>
<td>148.0 ± 121.0***</td>
<td>92.7 ± 81.8*</td>
<td>92.7 ± 81.8*</td>
</tr>
<tr>
<td>% change Ees from baseline</td>
<td>62.0 ± 90.9</td>
<td>35.6 ± 73.6</td>
<td>13.0 ± 39.0</td>
<td>13.0 ± 39.0</td>
</tr>
</tbody>
</table>

*\( p < 0.05 \), ***\( p < 0.001 \) as compared with baseline value.
sensitive index of global ventricular function. However, the proposal of the MPI being a reflection by changes in $dP/dt_{\text{max}}$ is inconsistent. Furthermore, the index was significantly affected by preload reduction and afterload increase.

### Sensitivity to changes in inotropy

Although the systolic index $Ees$ has been shown to be relatively insensitive to changes in inotropy, when compared to $dP/dt_{\text{max}}$ for example, it is highly resistant to changes in loading conditions. Despite this insensitivity to contractile change, there was a significant change in $Ees$, but no significant difference in the MPI with dobutamine. It could be argued that the MPI was unchanged due to the concomitant improvement in diastolic function as reflected by changes in $dP/dt_{\text{min}}$. This argument does not, however, support the proposal of the MPI being a sensitive index of global ventricular function.

In contrast to our data, Harada et al. were able to show a significant change in the MPI during low dose dobutamine infusion (5 µg/kg/min) in children who had undergone previous closure of ventricular septal defects ($n = 8$) and children with a history of Kawasaki disease but normal coronary arteries ($n = 7$). Interestingly, the MPI was significantly elevated at rest in this group of patients compared with normal reference values, suggesting resting myocardial dysfunction. The findings of a study examining the utility of the MPI in predicting which patients would display an ischaemic response to dobutamine stress however appear to be in agreement with our findings. In patients without ischaemia, there was little change in the MPI with increasing stress (0.53 ± 0.013 at rest vs 0.52 ± 0.16 at peak stress; $n = 14$), although the statistical analysis for this is not provided. These differences underscore the difficulty in interpreting changes in an index which relies on components, each of which may be variably affected by an intervention, or disease state.

### Load dependency of the MPI

In a non-invasive study in adults, Moller et al. showed the MPI to be dependent on preload in normal subjects but not in patients with previous myocardial infarction. In the normal subjects, preload reduction was shown to cause a decrease in ejection time but have limited effect upon isovolumic contraction time causing a significant increase in the index. In patients with previous infarction however, there were decreases in both of these time intervals leading to no change in the MPI.

Interestingly, the MPI was unaffected by a preload increase causing an 8.6% increase in left ventricular volume. This is in contrast to the approximately 20% reduction in left ventricular volume and 40% increase in arterial pressure with preload reduction and afterload increase, respectively. Whether larger degrees of preload increase would have produced a significant change in the MPI is uncertain, but changes in the index associated with, for example diuretic or antihypertensive therapy cannot be interpreted as altered myocardial function.

### Isovolumic index

The concept of a global index of ventricular function based on echocardiographically derived systolic and diastolic time indices was first proposed by Mancini et al., in 1982. Using equipment available in that era, the index was calculated using a combination of time intervals derived from M-mode assessment of the mitral valve with simultaneous carotid arterial pulse tracing and electrocardiogram. In a series of invasive studies, the index was shown to be dependent upon loading conditions but did not vary with changes in heart rate (range 129–177 beats/min). The Tei index, as it has become known is conceptually identical, but derived from Doppler measurements of ventricular inflow and outflow. This confers the advantage of potential application to analysis of right ventricular performance, congenital heart diseases, and situations where M-mode assessment and arterial pulse tracings are impractical. It appears however to be prone to the same limitations as the isovolumic index as proposed by Mancini.

### Study limitations

Because this was an animal study of the acute effects of interventions on the MPI we cannot exclude the possibility that chronic adaptations in patients may lead to different responses to changes in loading conditions. Furthermore, we cannot exclude the possibility that general anaesthesia may have modulated myocardial performance. Despite these potentially confounding variables however, our experimental preparation allows acquisition of data during apnoea and at fixed heart rates, both of which are manoeuvres that significantly reduce the variability in Doppler flow measurements present in the clinical setting, and thus improves the accuracy of...
measurements. In view of the small number of animals studied however, the possibility of false positives cannot be excluded. Furthermore, since multiple interventions were performed for each animal, the statistical analysis must be interpreted with caution. Since this was not a comparative study, the results cannot be unambiguously attributed to the changes in conditions, i.e., they could be due to underlying conditions and as such care should be taken with the interpretation and conclusion of the results. This is, however, a potential confounding factor in any study, apart from in double-blind randomized studies.

The basal pacing rate in our study was 140 bpm which is relatively fast when compared with adult human studies. The resting heart rate of our animals was approximately 120–130 bpm however and in order to have a consistent basal rate for all animals we chose 140 bpm. There is no reason why this would influence the validity of our documented responses to interventions, although clearly the range of changes in heart rate seen in the clinical situation may exceed those demonstrated here.

Interestingly, in this study there were no detectable changes in contractile indices with esmolol infusion at a rate of 1000 μg/kg/min. This is in contrast to our previous study of ventricular function using Danish Landrace pigs when depression of contractility was induced at the previous study of ventricular function using Danish Landrace pigs. This work was supported by an unrestricted educational grant from GE Vingmed Ultrasound, Horten, Norway and also by the Heart and Stroke Foundation of Canada. M.M.H.C. is supported by a Research Fellowship from the Heart and Stroke Foundation of Ontario.

References