Influence of Cardiac Function and Loading Conditions on the Myocardial Performance Index
– Theoretical Analysis Based on a Mathematical Model –

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Background: The myocardial performance index (MPI) has emerged as a Doppler-derived index for global ventricular function capable of estimating combined systolic and diastolic performance. While several studies have reported its load-dependency, responses of the MPI to various hemodynamic changes have not been fully characterized.

Methods and Results: The response characteristics of the MPI were examined and compared with ejection fractions (EF) by changing hemodynamic parameters within the physiological range in a lumped parameter model of the cardiovascular system. At baseline, the MPI was 0.42 and the EF was 0.68. Heart rate increase resulted in a decrease in EF and an increase in the MPI. Reduction in end-systolic elastance decreased EF and increased the MPI. Volume overload and ventricular stiffening did not affect EF but paradoxically reduced the MPI. Increased afterload due to higher systemic resistance resulted in a decrease in EF and increase in the MPI, but afterload increase caused by reduced arterial compliance led to a decrease in both EF and MPI. These MPI characteristics caused paradoxical improvement of the MPI during disease progression of chronic heart failure in a simulation of mitral regurgitation.

Conclusions: The MPI is affected by a wider variety of hemodynamic parameters than EF. In addition, it is predicted to decrease paradoxically with volume overload, reduction in arterial compliance, or ventricular diastolic stiffening. These MPI characteristics should be considered when assessing cardiovascular dynamics using this index. (Circ J 2016; 80: 148–156)

Key Words: Blood volume; Contractility; Echocardiographic parameter; Heart failure; Mitral regurgitation

Heart failure involves impairment of systolic and diastolic function to various degrees, in association with various degrees of altered heart rates and cardiac loading conditions. Conventional echocardiographic indices that are routinely applied in the assessment of ventricular function have a number of limitations. The ejection fraction (EF), one of the most frequently used markers of systolic function, is known to be load-dependent and results in considerable inaccuracies when the cardiac chamber is deformed into a spherical shape.1 Also, transmitral flow, a commonly used indicator of diastolic function, can exhibit a pseudonormal filling pattern.2,3 The myocardial performance index (MPI), also called the Tei index, defined as the sum of the isovolumic contraction time (ICT) and the isovolumic relaxation time (IRT) divided by the ejection time (ET), has emerged as a parameter for global ventricular function capable of estimating combined systolic and diastolic performance.4 The MPI is easily obtained and reproduced because it only utilizes cardiac intervals. This index has been shown to be sensitive to contractile change in clinical studies, and it is used in the early detection of ventricular dysfunction.5,6 Moreover, it has better prognostic value than EF in patients with dilated cardiomyopathy and amyloidosis.7–9

While MPI has been shown to correlate with invasive systolic and diastolic measurements, such as peak dP/dt and ventricular stiffness, it remains uncertain whether it is a
surrogate phenomenon or whether it has a direct functional relevance. Furthermore, limitations in using the MPI in some clinical settings, owing to load dependence, have been reported. In fact, previous animal and human studies reported conflicting results regarding load dependency of the MPI. These inconsistencies can partly be due to the fact that in vivo studies, it is virtually impossible to alter only one component of the hemodynamic status and assess its independent effect on the MPI. Computer simulation has the advantage in this regard because it enables us to quantify the genuine effect of change in a single hemodynamic component on cardiac indices.

Therefore, we sought to examine comprehensively the effect of changes in cardiac systolic and diastolic function, loading conditions, and heart rates on the MPI using a well-established mathematical cardiovascular system model, especially to compare the MPI with EF. Additionally, to better characterize the MPI in the clinical practice, we simulated a clinical scenario of heart failure and examined the change in the MPI during the progression of heart failure.

**Methods**

**Cardiovascular Model**

We developed a lumped parameter model of the cardiovascular system, as shown in Figure 1. Both systemic and pulmonary circulations were modeled based on modified 3-element Windkessel impedances using capacitances, proximal characteristic resistances, and peripheral resistances. Atrial and ventricular chambers were modeled based on the modified time-varying elastance model. The ventricular model assumes a non-linear end-diastolic pressure-volume relationship (EDPVR) and a linear end-systolic pressure-volume relationship. End-diastolic pressure (Ped) and volume (Ved) are interrelated by:

\[
\text{Ped} = A \times \{\exp[B \times (Ved - Vo)] - 1\} \quad (1)
\]

and

\[
\text{Pes} = \text{Ees} \times (\text{Ves} - \text{Vo}) \quad (2)
\]

where Ees is the maximal elastance. Ventricular function is modeled as a modified time-varying elastance model:

\[
P(V(t), t) = \text{Ev}(t) \times (\text{Pes}(V(t)) - \text{Ped}(V(t))) + \text{Ped}(V(t)) \quad (3)
\]

where Ev(t) is the normalized time-varying elastance. Suga et al demonstrated that the normalized elastance curve was fairly independent of the loading conditions, contractile state, and heart rate in isolated canine hearts. The normalized elastance curve in humans was reported by Senzaki et al, and it was

<table>
<thead>
<tr>
<th>Table. Baseline Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary</strong></td>
</tr>
<tr>
<td>Arterial pressure (mmHg)</td>
</tr>
<tr>
<td>Mean venous pressure (mmHg)</td>
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<td>End-systolic pressure (mmHg)</td>
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<td>End-diastolic pressure (mmHg)</td>
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<td>End-diastolic volume (ml)</td>
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<tr>
<td>Ejection fraction (%)</td>
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<td>Cardiac output (L/min)</td>
</tr>
<tr>
<td>Effective arterial elastance (mmHg/ml)</td>
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<tr>
<td>Left ventricular echocardiographic parameters</td>
</tr>
<tr>
<td>Isovolumic contraction time (ms)</td>
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<td>Ejection time (ms)</td>
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<tr>
<td>Isovolumic relaxation time (ms)</td>
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<tr>
<td>Myocardial performance index</td>
</tr>
<tr>
<td>Transmitral E wave (m/s)</td>
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<td>Transmitral A wave (m/s)</td>
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Figure 1. Schematic representation of the cardiovascular model. AV, aortic valve; LA, left atrium; LV, left ventricle; MV, mitral valve; PV, pulmonary valve; RA, right atrium; RV, right ventricle; TV, tricuspid valve.
QT interval = 0.243 + 0.145 × \frac{60}{\text{Heart rate}} \quad (5)

For atrial chambers, a simpler time-varying elastance model was used:

\[ P[V(t), t] = E_{\text{at}}(t) - \left[ E_{\text{es}}(V(t)) - E_{\text{ed}}(V(t)) \right] + E_{\text{ed}}(V(t)) \quad (6) \]

\[ E_{\text{at}}(t) = 0.5 \times \left[ 1 - \cos \left( \frac{\pi t}{T_{\text{max}}} \right) \right] \quad (7) \]

\[ E_{\text{es}} = E_{\text{max}}(V_{\text{es}} - V_{\text{vo}}) \quad (8) \]

\[ E_{\text{ed}} = E_{\text{min}}(V_{\text{es}} - V_{\text{vo}}) \quad (9) \]

where \( E_{\text{max}} \) and \( E_{\text{min}} \) are the maximal and minimal atrial elastances, respectively.\(^{22}\)

Inlet and outlet valves were represented as diodes that permitted

Ev(t) = \begin{cases} 1 - \exp \left( -\frac{t}{T_{\text{max}}} \right) & \text{for } t < T_{\text{max}} \\ 1 - \exp(-1) & \text{for } T_{\text{max}} \leq t < 1.05T_{\text{max}} \\ \cos + 10.5 \times \frac{t}{T_{\text{max}}} & \text{for } t \geq 1.05T_{\text{max}} \end{cases} \quad (4)

where \( T_{\text{max}} \) and \( \tau \) represent the time to maximal elastance and relaxation time constant, respectively. \( T_{\text{max}} \) was assumed to be proportional to the QT interval (\( T_{\text{max}} = 0.95 \times \text{QT interval} \)), which was expressed as a function of the heart rate.\(^{21}\)

\[ \text{QT interval} = 0.243 + 0.145 \times \frac{60}{\text{Heart rate}} \quad (5) \]
Load-Dependency of the Tei Index

Flow in only one direction. The pressure-flow relationship across an inlet valve was assumed to follow the Bernoulli law. Additionally, taking into account the contribution of blood inertia, the pressure drop written as a function of flow (Q) is:

\[ \Delta P = \frac{1.06}{2*1.333*A_{\text{avr}}^2} \times Q |Q| + L_{\text{avr}} \times Q^2 \times 1.333 \times A_{\text{avr}}^2 \]  

where \( A_{\text{avr}} \) is the time-varying atrioventricular valve area and \( L_{\text{avr}} \) is the coefficients of inertial terms. The time-course of the \( A_{\text{avr}} \) was assumed to be independent of flow:

\[ A_{\text{avr}} = \begin{cases} \text{EOA} & \text{atrial pressure} > \text{ventricular pressure} \\ 0 & \text{atrial pressure} = \text{ventricular pressure} \\ \text{EROA} & \text{atrial pressure} < \text{ventricular pressure} \end{cases} \]  

where EOA and EROA are the effective orifice area and effective regurgitant orifice area, respectively. EROA was 0 cm² in normal circulation and was set at 0.2 cm² in the presence of moderate atrioventricular regurgitation.

The unstressed blood volume was defined as the maximum blood volume within a capacitive vessel without raising its pressure above 0 mmHg. The blood volume exceeding the unstressed volume was defined as stressed volume. The pressure within the compartment rises linearly with stressed volume in relation to the compliance:

\[ \text{Total blood volume} = \text{unstressed blood volume} + \text{stressed volume} \]  

\[ \text{Pressure} = \frac{\text{stressed volume}}{\text{compliance}} \]  

The baseline values of each parameter for a 70-kg man...
adapted from previous reports are listed in Table S1. Effective arterial elastance was calculated as the Pes divided by the stroke volume. The MPI for the left ventricle (LV) was defined as $(\text{ICT}+\text{IRT})/\text{ET}$. The model was constructed using Matlab and Simscape (MathWorks, Inc). The governing equations of the model were solved based on the implicit numerical differentiation formulas.

Protocols

1. **Simulation of Known Pharmacological Effects on the MPI for the Model Validation** To evaluate the validity of the model in predicting the changes in the MPI, model-predicted and reported changes in the MPI upon pharmacological manipulation were compared. Parameters for LV systolic and diastolic function as well as heart rate were changed by simulating dobutamine and esmolol infusion in accordance with a previous animal study, which reported that the MPI decreased by 25% upon dobutamine infusion and increased by 37% upon esmolol infusion. Systemic vascular resistance was assumed to decrease by 25% with dobutamine infusion.

2. **Response Characteristics of the MPI to Changes in Various Hemodynamic Parameters** The parameters for LV contractility, LV diastolic function, LV afterload, preload, and heart rate were changed in the cardiovascular model within physiological ranges (Table S2). The corresponding changes in the LV MPI and EF were examined to determine response characteristics of the MPI, especially in comparison with EF.

3. **Clinical Scenario With Chronic Mitral Regurgitation** As an example of change in the MPI, a clinical scenario of heart failure progression with chronic mitral regurgitation was simulated. At baseline, the EROA was set at 0.2 cm$^2$; total stressed volume, at 760 ml; and end-systolic elastance, at 2.5 mmHg/ml. Further reduction in systolic function (end-systolic elastance=2 mmHg/ml) followed by development of diastolic dysfunction (exponent for EDPVR=0.033/ml and stressed volume=860 ml) were introduced into the mitral regurgitation model.

**Results**

Baseline cardiovascular indexes obtained from the simulation using the baseline parameter values are shown in Table. The arterial pressure was 100/61 mmHg and the cardiac output was 4.86 L/min. The MPI was 0.42 and EF was 0.68 at baseline. The model reproduced normal human values for the MPI and EF shown in previous studies (0.39±0.05 and ≥0.55, respectively). Similarly, a simulation of esmolol infusion (+25%, +38%, −25% and +25% from the baseline, respectively), total isovolumic time and the MPI decreased by 24.2% and 23%, respectively. Similarly, an increase in systemic resistance caused ICT and IRT prolongation, and thus, an increase in the MPI, while ET did not change in response to preload augmentation (+0.03% to −0.04% change).

**Simulation of Pharmacological Effects**

When heart rate, LV end-systolic elastance, LV relaxation time constant and systemic resistance were changed in accordance with the previous animal studies to simulate dobutamine infusion (+25%, +38%, −25% and +25% from the baseline, respectively), total isovolumic time and the MPI decreased by 24.2% and 23%, respectively. Similarly, a simulation of esmolol infusion, represented by change in heart rate, end-systolic elastance, and LV relaxation time constant by −11%, −57% and +75%, respectively, resulted in 39.5% prolongation in total isovolumic time and a 36.9% increase in the MPI. Thus, our model accurately reproduced quantitative changes in the MPI in response to dobutamine and esmolol infusion in vivo (−25% and +37%, respectively).

**Response Characteristics of the MPI to Changes in Various Hemodynamic Parameters**

**Preload Dependency** An increase in blood volume resulted in elevation of LV diastolic pressure, which led to IRT shortening. ET did not change in response to preload augmentation (Figure 2A). Consequently, volume load resulted in reduction in the MPI. The MPI exhibited +5.8% to −15.5% changes from the baseline in response to −21.9% to +87.5% changes in blood volume (Figure 3A), whereas EF was not affected by preload (+0.03% to −0.04% change).

**Afterload Dependency** The responses of the MPI and EF differed depending on various types of afterload changes. Elevation in systemic resistance caused ICT and IRT prolongation, ET shortening, and thus, an increase in the MPI, while higher effective arterial elastance due to higher systemic resistance led to a reduction in EF (Figure 2B). The amplitude of change corresponding to systemic resistance variations within the physiological range was 3.3-fold greater in the MPI than in EF (−27.3% to +63.4% change in the MPI and +11.6% to −19.0% change in EF, Figure 3B), indicating that the MPI was more sensitive to change in systemic resistance than EF.

In contrast to augmentation in systemic resistance, the MPI...
Effects of Contractility and Diastolic Function

Increase in LV contractility (end-systolic elastance) improved both the MPI and EF (Figures 3E). An increase in the LV relaxation time constant caused a steady increase in IRT and an increase in the MPI (Figure 2F), whereas a change in the LV relaxation time constant did not affect EF (Figure 3F).

A higher LV stiffness coefficient resulted in lower Pes and higher LV diastolic pressure, leading to shortened IRT and paradoxical improvement (reduction) of the MPI. The EF was not influenced by a change in the EDPVR. Thus, ventricular stiffening only affected the MPI. There was a positive correlation between MPI and cardiac output; however, there was no
correlation with change in other parameters, such as stressed volume, systemic resistance, and end-systolic elastance (Figure 3G).

Heart Rate Dependency Heart rate increase resulted in an MPI increase, while an EF decrease resulted from a reduction in end-diastolic volume with increased heart rate (Figure 3H).

Figure 4 shows the relationship between echocardiographic parameters and ventricular-arterial coupling represented by the ratio between ventricular and arterial elastance (Ea/Ees). Similarly to the EF, the MPI reflected a change in Ea/Ees in response to change in systemic resistance, arterial compliance end-systolic elastance and heart rate, but the coefficient of regression differed considerably depending on the hemodynamic parameters that were changed.

Right Ventricular MPI As shown in Figure 5, the behavior of right ventricular MPI in response to various hemodynamic changes was similar to that of left ventricular MPI. The only exception was that, contrary to left ventricular MPI, volume overload resulted in increased right ventricular MPI reflecting the increase in right ventricular afterload due to elevated left atrial pressure.

Clinical Scenario With Chronic Mitral Regurgitation

The baseline regurgitant fraction of mitral regurgitation was 34%. Arterial pressure was 95/55 mmHg; LV end-diastolic pressure, 12 mmHg; and cardiac output, 4.41 L/min at baseline. Compared with the normal circulation without mitral regurgitation, the MPI increased to 0.29 and the EF decreased to 0.68. However, further development of diastolic dysfunction (enhanced LV stiffness) resulted in elevation of LV end-diastolic pressure, paradoxical reduction in the MPI and no change in EF (Figure 6).

Discussion

The present study has revealed several important characteristics of the MPI in response to changes in various cardiovascular properties; (1) the MPI is highly sensitive to changes in preload, afterload, systolic and diastolic function (ie, contractility, ventricular relaxation, and ventricular stiffening), and heart rate; (2) static and pulsatile afterload have opposite effects on the MPI; (3) the MPI responds differently to diastolic dysfunction caused by impaired LV relaxation and by LV diastolic stiffening; and (4) hemodynamic changes that are expected to occur in parallel with heart failure progression (ie, ventricular systolic and diastolic dysfunction and abnormal arterial loading) do not affect the MPI in the same way. While the MPI increases with reduction in end-systolic elastance, impairment of LV relaxation, and elevation of systemic resistance, the MPI is predicted to decrease paradoxically if volume overload, reduction in arterial compliance, or ventricular diastolic stiffening occurs secondary to further disease progression. Special attention needs to be given while using the MPI when several types of hemodynamic changes develop concomitantly, because the MPI is predisposed to pseudonormalization.

The interaction between ventricular and arterial systems is a key determinant of cardiovascular performance. Sunagawa et al proposed a simplified framework where stroke volume is determined by ventricular-arterial coupling, defined as the ratio between ventricular and arterial elastance (Ea/Ees):26

\[
\text{Stroke volume} = \frac{\text{Ved} - \text{Vo}}{1 + \text{Ea/Ees}}
\]

Clinical applicability of this framework has been confirmed in a number of studies. In fact, EF, an established marker of global LV function, is closely connected to ventricular-arterial coupling because it can be described as follows:

\[
\text{EF} = \frac{\text{Stroke volume}}{\text{Vo}} - \frac{1}{1 + \text{Ea/Ees}} \frac{\text{Ved}}{1 + \text{Ea/Ees}}
\]

The MPI positively correlates with ventricular-arterial coupling in most settings. Compared with EF, the MPI is more sensitive to change in systemic resistance, a major determinant of ventricular-arterial coupling.26 However, as shown in Figure 4, the direction of the correlation between the MPI and Ea/Ees differs considerably depending on the parameters that are changed, suggesting that estimating change in Ea/Ees based on the MPI is difficult. For instance, an increase in Ea/Ees caused by increased systemic resistance results in an increase in the MPI, while an increase in Ea/Ees due to reduced arterial compliance leads to a decrease in the MPI. Thus, it is possible that the MPI underestimates Ea/Ees, when reduction in arterial compliance occurs in addition to an increase in systemic resistance, which can occur in the elderly or in those with heart failure with preserved EF.31-34

The MPI is highly sensitive to alterations in several types of hemodynamic parameters. The MPI is able to detect alterations in blood volume, ventricular relaxation, and stiffness, which cannot be detected by EF. Conversely, this highly sensitive nature of the MPI can lead to misinterpretation when several types of hemodynamic changes develop concomitantly. For example, volume overload, reduction in arterial compliance, and ventricular diastolic stiffening, which are commonly present in heart failure, result in a paradoxical decrease in the...
MPI. Thus, the MPI underestimates the degree of reduction in contractility when volume overload, reduction in arterial compliance, or ventricular stiffening is present. A good example of a clinical scenario with chronic mitral regurgitation is shown in Figure 6. The development of diastolic stiffening caused elevation of end-diastolic pressure and resulted in a paradoxical decrease in the MPI, which would lead to underestimation of the degree of systolic dysfunction. In contrast, expected maximal reduction in the MPI was only 15% from volume overload and 13% from reduction in arterial compliance (Figure 3). These effects are weaker than that from reduced contractility, as shown in Figure 3. Therefore, the MPI would be practically useful and would be able to detect a general trend of disease progression in heart failure until marked ventricular stiffening develops.

In contrast with the results of the present study, Zhang et al reported a positive correlation between the MPI and LV filling pressure in those with normal or restrictive mitral flow pattern, and suggested that the MPI does not pseudonormalize with elevated end-diastolic pressure.\(^{35,36}\) Our model predicted that the MPI increases in response to diastolic dysfunction relating to impaired relaxation, whereas it decreases with genuine diastolic LV stiffening. Thus, we speculate that a positive correlation between the MPI and LV filling pressure was observed in their study because those with elevated end-diastolic pressure happened to have impaired relaxation rather than LV stiffening.

**Study Limitations**

We used a lumped parameter model based on the 3-element Windkessel model as an approximation of the vascular system. While its input impedance is known to be reasonably similar to that of the natural vascular tree,\(^{37}\) this model does not account for reflection of pressure and flow wave, which may have partly contributed to the relatively low blood pressure at baseline in the present study. However, validation analysis revealed that the global change in the MPI in response to pharmacological intervention was similar to the results of a previous animal study.\(^{21}\)

**Conclusions**

The MPI globally represents ventricular-arterial coupling, but it is more affected by a wider variety of hemodynamic parameters than EF. While MPI is expected to increase in parallel with disease progression in heart failure, it is predicted to decrease paradoxically if volume overload, reduction in arterial compliance, or ventricular stiffening occurs as a process of further disease progression. These characteristics of the MPI should be fully taken into account when assessing cardiovascular dynamics using this index.

**Conflict of Interest**

None.

**Grant Support**

None.

**References**


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Supplementary Files

Supplementary File 1

Table S1. Baseline values of hemodynamic parameters

Table S2. Simulated change in parameters

Figure S1. Examples of change in hemodynamics and cardiac intervals in response to altered loading conditions or ventricular function.