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Myocardial performance index is sensitive to changes in cardiac contractility, but is also affected by vascular load condition

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Abstract*— Myocardial performance index (MPI), or Tei index, is measured by Doppler echocardiography in clinical practice. MPI has been shown to be useful in evaluating left ventricular (LV) performance and predicting prognosis in cardiac patients. However, the effects of LV load and contractile states on MPI remain to be thoroughly investigated. In 14 anesthetized dogs, we obtained LV pressure-volume relationship with use of sonomicrometry and catheter-tip manometry. MPI was determined from the time derivative of LV volume and pressure. LV end-systolic pressure-volume ratio (E_{es}'), effective arterial elastance (E_a) and LV end-diastolic volume (V_{ed}) were used as indices of LV contractility, afterload and preload, respectively. Hemodynamic conditions were varied over wide ranges [heart rate (HR), 66-192 bpm; mean arterial pressure, 71-177 mmHg] by infusing cardiovascular agents, by inducing ischemic heart failure and by electrical atrial pacing. Multiple linear regression analysis of pooled data (66 data sets) indicated that MPI (0.6-1.8) significantly correlated with E_{es}' [1.5-17.5 mmHg·ml^{-1}, $p<0.0001$, standard partial regression coefficient (β) =-0.66], E_a (3.6-21.9 mmHg·ml^{-1}, $p<0.001$, $\beta = 0.4$) and V_{ed} (11-100 ml, $p<0.0001$, $\beta = -0.69$). MPI directly correlated with the time constant of isovolumic relaxation (19-66 ms, $p<0.05$), but not with HR or LV diastolic-stiffness (all $p>0.1$). Theoretical analysis also indicated that MPI decreases following the increases in LV contractility and in preload, while it increases in response to an increase in LV afterload. We conclude that MPI sensitively detects changes in LV contractility. However, MPI is also affected by changes in LV afterload and preload.

I. Introduction

Noninvasive echocardiographic indices of ventricular function are of great clinical importance in diagnosing and managing heart disease. The Doppler myocardial performance index (MPI), also referred to as the Tei index, is easily obtainable and has been clinically useful in assessing global ventricular function [1]. MPI is derived from measured specific heart cycle intervals calculated as the single heart cycle (isovolumetric contraction time + isovolumetric relaxation time)/ejection time. Many investigators evaluated the mechanical determinants of MPI in animals and in patients [2-6]. The effect of left ventricular (LV) load and contractile states on MPI is, however, still a controversial issue. The purpose of this study was to clarify the mechanisms that regulate the magnitude of MPI in rigorously controlled animal experiments, which is not possible in humans.

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II. Methods

A. Animal

We used 14 adult mongrel dogs (both sexes; weight, 20–30 kg). The investigation conformed with the Guide for the Care and Use of Laboratory Animals. All protocols were approved by the Animal Subjects Committee of the National Cerebral and Cardiovascular Center. Observations of LV function (but not MPI) from these animals were included in our previous report [7].

B. Preparation

After anesthesia was induced with sodium pentobarbital (25 mg/kg), the animals were intubated endotracheally and ventilated artificially. An appropriate level of anesthesia was maintained by continuous inhalation of 1.5% isoflurane. A fluid filled catheter (8F) was placed in the right femoral artery to measure systemic arterial pressure (AP). After a median sternotomy, the heart was suspended in a pericardial cradle. A pair of pacing electrodes was fixed at the right atrial appendage for atrial pacing. A catheter-tipped micromanometer (PC-751, Millar Instruments, Houston, TX) was inserted via the LV apex to measure LV pressure (LVP). As depicted in Fig. 1A, ten sonomicrometer crystals were implanted in the subepicardium of LV and the right side of the interventricular septum to obtain LV dimensions. Surface ECG was recorded. After the instrumentation was completed, the pericardium was closed. All data acquisitions were done at end-expiration. Analog signals of AP, LVP, sonomicrometric LV dimensions, and ECG were digitized at 200 Hz and stored in the computer for off-line analysis.

C. Experimental protocols

After the initial preparation and surgical procedures were complete, the animals were allowed to stabilize for 30 min. Under steady-state baseline condition, we recorded the analog signals for about 10 sec in each animal. After obtaining the hemodynamic data at baseline condition, we created various hemodynamic conditions as described in the following protocols. In each intervention, we waited for 20 min to confirm that hemodynamic conditions reached steady-state.

Protocol 1 (n=8): Hemodynamic data were recorded while LV contractility was increased by dobutamine infusion (5

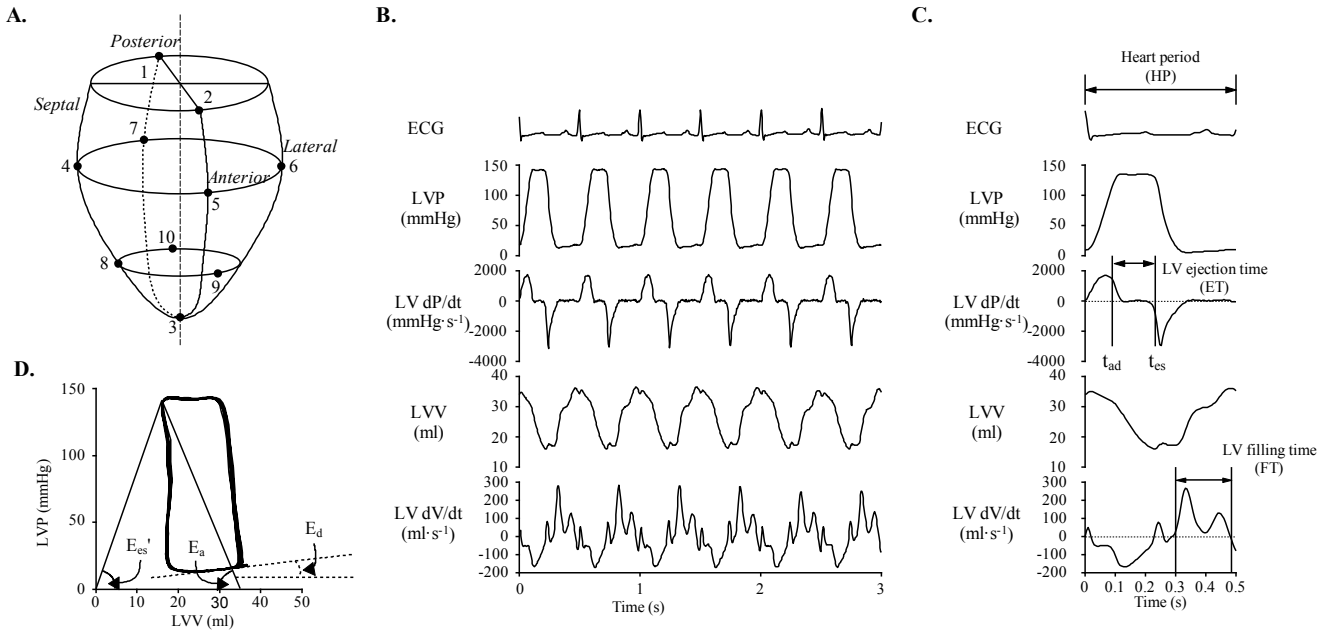

Fig. 1. **A**, placement of sonomicrometric crystals on left ventricular (LV) epicardium. **B**, time traces of hemodynamic variables. LVP, LV pressure; LV dP/dt, time derivative of LVP; LVV, LV volume; LV dV/dt, time derivative of LV volume. **C**, definitions of cardiac time periods. t_{es}, end-systole; t_{ad}, end of isovolumic contraction.**D**, definitions of cardiovascular parameters in LV pressure volume loop

$\mu g \cdot kg^{-1} \cdot min^{-1}$). After the data were recorded, dobutamine infusion was temporarily suspended. We created acute heart failure (AHF) by embolizing the left coronary artery with glass microspheres (90 μm in diameter). Data recording was repeated under depressed LV contractility. Hemodynamic data were also recorded after LV contractility was restored by reinfusion of dobutamine.

Protocol 2 (n=6): Hemodynamic data were recorded after pharmacologically altering vascular resistance (afterload) and LV filling (preload) by infusing norepinephrine (0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$), sodium nitroprusside (3 $\mu g \cdot kg^{-1} \cdot min^{-1}$), or 250 ml of 10% dextran 40. The possible dependence of MPI on heart rate (HR) was tested by suppressing the intrinsic atrial beat using zatebradine (UL-FS49, 0.5 $mg \cdot kg^{-1}$) and instituting atrial pacing to obtain hemodynamic data at different HR (±25% of baseline HR).

At the conclusion of the experiments, we euthanized the dogs with an intravenous injection of pentobarbital and potassium chloride, and verified the position of the sonomicrometer crystals and catheters. LV myocardium volume (LVMV) was measured by water displacement in a volumetric cylinder.

D. Data analysis and Statistics

LV volume calculation using sonomicrometric LV dimensions: The three-dimensional position of each crystal was defined as a function of time based on the distances between the crystals [7]. The LV epicardial volume (including LV cavity volume and LVMV) was estimated using a software that applied an ellipsoidal shell model to the coordinates of all 10 crystals (Fig. 1A). LV cavity volume (LVV) was obtained by subtracting LVMV from the estimated LV epicardial volume [7]. Time traces of ECG, LVP, the time derivative of LVP (LV dP/dt), LVV and the time derivative of LVV (LV dV/dt) are shown in Fig. 1B.

MPI and Cardiovascular parameters: End-systole (t_{es}) was defined as the time when LV dP/dt decreased to 20% of its minimum (Fig. 1C). The end of isovolumic contraction phase (t_{ad}) was defined as the moment when LV dP/dt decreased to 80% of its maximum, according to previous study [7]. LV ejection time (ET) was obtained by subtracting t_{ad} from t_{es}. LV filling time (FT) containing early and late filling profiles was determined from the trace of LV dV/dt (Fig. 1C). MPI was calculated with use of the following formula,

$$\mathrm{MPI} = \frac{\mathrm{HP} - \mathrm{FT} - \mathrm{ET}}{\mathrm{ET}}$$

where HP is heart period. LV contractility was indexed by the end-systolic pressure (P_{es})-volume (V_{es}) ratio ($E_{es}' = P_{es} / V_{es}$) (Fig. 1D). End-diastolic volume (V_{ed}) was defined as LV volume at the peak of R wave on ECG , and used as an index of LV preload. Effective arterial elastance (E_a) was defined as the ratio of P_{es} to stroke volume ($SV=V_{ed}-V_{es}$) (Fig. 1D), and used as an index of LV afterload. LV diastolic stiffness was indexed by diastatic pressure-volume relation (E_d) [8] (Fig. 1D). LV relaxation was indexed by time constant of LV pressure decay during isovolumic relaxation (τ).

All data are presented as mean ± SD. The associations among variables were analyzed using a mixed-model procedure to handle the dependencies in repeated measurements within the same animal. Coefficient of determination (R^2) was used to evaluate the strength of association, since it measures how much variability of the dependent variable is the result of the independent variable. A p value less than 0.05 was considered statistically significant.

III. Results

A total of 66 data sets of MPI, and cardiovascular parameters were obtained from protocol 1 and 2, where the hemodynamic condition was varied over wide ranges (HR, 66-192 bpm; AP, 71-177 mmHg). Fig. 2 shows univariate relationships between MPI and each of the cardiovascular parameters. MPI correlated significantly and negatively with E_{es}', positively with E_a and negatively with V_{ed} (Fig. 2A, B, C). MPI did not significantly correlate with E_d (Fig. 2D). MPI and τ were significantly correlated (Fig. 2E). MPI and HR were not significantly correlated (Fig. 2F).

Multiple linear regression analysis indicated that MPI significantly correlated with E_{es}' ($p<0.0001$, standard partial regression coefficient (β) =-0.66), E_a ($p<0.001$, β =0.4) and V_{ed} ($p<0.0001$, β=-0.69).

We performed simple theoretical analysis to validate the present experimental findings. We approximated LVP during isovolumic period to the following sinusoidal function [9],

$$LVP = \frac{1}{2} P_{max}\left(1 - \cos(t \cdot \frac{\pi}{0.18})\right) + P_{ed}$$

P_{max}, the maximum of isovolumic LVP, reflects LV contractility. P_{ed}, LV end-diastolic pressure, reflects LV preload. We approximated LVP during ejection period to hypothetically constant AP, which reflects LV afterload. Ejecting beat LVP assumed a trapezoidal shape as shown in Fig. 3. Compared to MPI (0.96) in baseline condition (Fig. 3A), increase in P_{max} decreased MPI (0.62) (Fig. 3B). Increase in AP increased MPI (1.86) (Fig. 3C). Increase in P_{ed} decreased MPI (0.78) (Fig. 3D). In accordance with our experimental results, MPI decreased following the increase in LV contractility and in LV preload, while MPI increased following the increase in LV afterload.

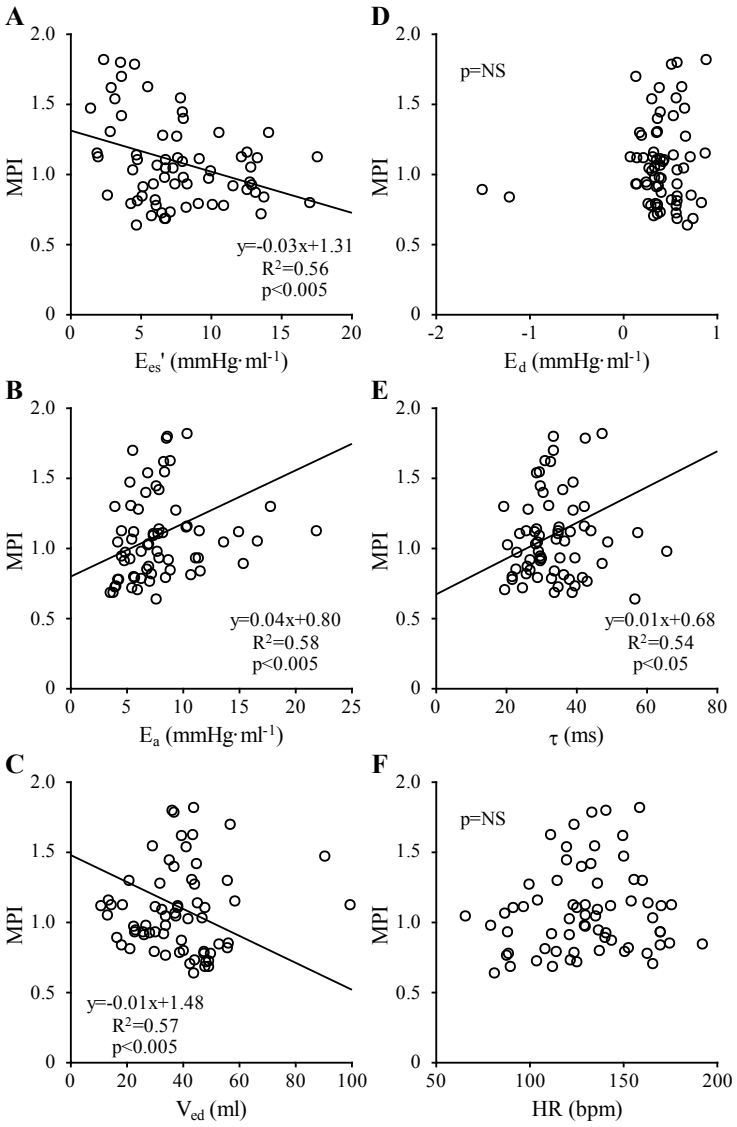

Fig. 2. Relationships between MPI and E_{es}' (**A**), E_a (**B**), V_{ed} (**C**), E_d (**D**), τ (**E**), and HR (**F**). Each panel shows raw data from all interventions (66 data points) and the line represent-ing the population-averaged regression between MPI and the cardiovascular parameters, regression equation, R^2, and probability value.

IV. Discussion

Our extensive analysis demonstrates that MPI can reliably detect alterations in LV contractile function induced by inotropic modulation and induction of ischemic heart failure. MPI correlated favorably with invasive hemodynamic pressure-volume loop measurements of LV contractile state and diastolic relaxation in an experimental animal model. We also observed that MPI was directly affected by acute changes in preload and afterload induced by infusions of vasoconstrictor, vasodilator and volume expander. Theoretical analyses validated these experimental results.

The conventional MPI, first described by Tei et al., is based on the recording of both mitral and aortic flows using pulsed Doppler [1]. MPI has been suggested to be a unique index of both systolic and diastolic (global) ventricular function. In this study, we noted that MPI correlated with indices of LV systolic contractility and LV relaxation. In contrast, Cheung et al. demonstrated that MPI was unable to consistently detect acute changes in contractile function [4]. However, if they correlated MPI and the contractility indices spanning from reduced to enhanced contractile condition, they might have detected significant correlation between MPI and the contractility indices as in the present study. We found that MPI and E_d were not significantly correlated. E_d reflects passive and late diastolic myocardial property of LV [8]. In contrast, LaCorte et al. reported that MPI significantly correlated with LV stiffness constant derived from LV end-diastolic pressure volume relationship (EDPVR) [5]. Differences in the analyzed index, E_d vs LV stiffness constant from EDPVR, or experimental conditions, volume loading vs inferior vena cava occlusion, might cause the discrepant findings between present and previous studies. Because E_d is not coupled to a contracted atrium, it conveys passive LV stiffness better than the EDPVR [8]. Although we cannot

completely exclude

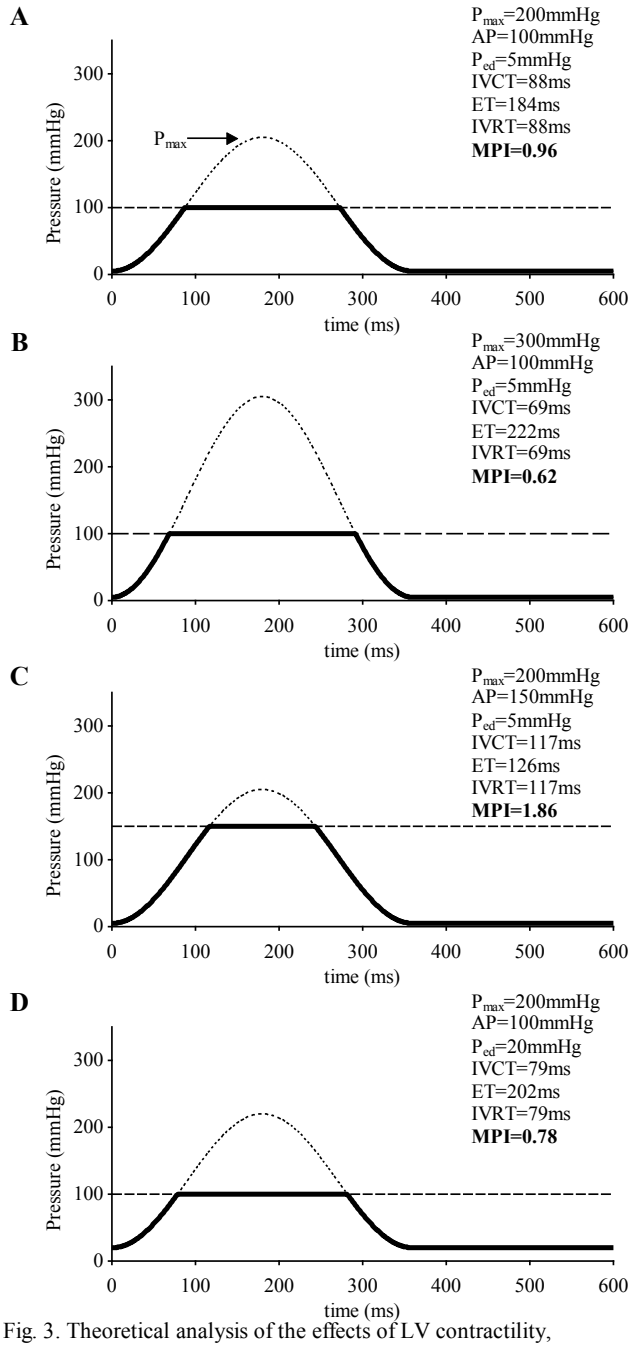

Fig. 3. Theoretical analysis of the effects of LV contractility, afterload and preload on MPI. Dotted sinusoidal line indicates isovolumic LVP, whose peak is P_{max}. Dashed horizontal line indicates AP. Bold trapezoidal line indicates ejecting beat LVP. IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time. In IVCT and IVRT, dotted and bold lines are overlapped. In comparison to Baseline in **A**, P_{max} is increased in **B**, AP is increased in **C**, and P_{ed} is increased in **D**.

significant contributions of LV late diastolic myocardial properties to MPI, their effects may be small and effectively negligible compared with the status of LV systolic contractile function and loading conditions.

Dependence of MPI on LV preload and afterload noted in this study is compatible with the previous clinical and experimental findings [2-6, 10]. Previous experimental study suggested that MPI was significantly affected by the respiratory condition [10]. Although MPI may be used as a sensitive index reflecting LV systolic function, it may be substantially affected by extracardiac condition including vascular load and respiratory condition in vivo.

In analyzing the experimental data, we relied on E_{es}' (the end-systolic pressure-volume ratio) to quantify LV contractility, which can be evaluated more precisely by both the slope (E_{es}) and volume axis intercept (V_0) of the end-systolic pressure–volume relationship. It was unclear how each of them contributes to the magnitude of MPI in this study. Despite these limitation, the end-systolic pressure-volume ratio as a single contractile index simplifies the statistical analysis of contractility.

V. Conclusion

MPI sensitively detects changes in LV contractility. However, MPI is also affected by changes in LV afterload and preload. MPI may have limitations in clinical scenarios associated with rapidly changing hemodynamic conditions.

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