Noninvasive Doppler-derived myocardial performance index in rats with myocardial infarction: validation and correlation by conductance catheter

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THE UNDERSTANDING OF THE PROGRESSIVE structural and molecular cardiac changes after myocardial infarction (MI) is of major interest to the cardiovascular research community (11, 24). It may indeed contribute to the development of new therapeutic modalities for heart failure (17). The changes in cardiac structure and function in the follow-up of MI can be assessed by using different techniques, including both invasive [conductance catheter (CC)] and noninvasive [transtracheal echocardiography (TTE)] approaches (2, 27). Among other advantages, the noninvasive echocardiographic methodologies are certainly appealing for long-term follow-up protocols. In addition, TTE is an established clinical diagnostic tool (22).

Several structural and functional parameters can be assessed by using TTE, such as myocardial wall thickness, end-systolic and -diastolic volumes, left ventricular (LV) mass, ejection fraction (EF), fractional shortening, and velocity of circumferential fiber shortening (Vcf). The myocardial performance index (MPI) is a relatively recent parameter combining both systolic and diastolic functions. MPI is the ratio of total time spent in isovolumic activity (isosvolumic contraction and relaxation times) to the ejection time (ET) and is measured from the mitral inflow and LV outflow time intervals. Recently, in a clinical setting, the MPI has been described as a predictor of cardiovascular mortality, independent of other measurements of cardiac function (EF and wall motion score index) and of traditional cardiovascular risk factors (smoking, diabetes, hyperlipidemia, and hypertension) in elderly men (1). Additionally, it correlates to plasma brain natriuretic peptide in patients with hypertrophic cardiomyopathy (15). It is an attractive parameter because it appears to be independent of the LV shape. Indeed, the measurement of the LV dimensions is not mandatory. It has been reported that MPI correlates with the peak positive value of the time derivative of LV pressure (dP/dtmax) and the time constant of relaxation derived from the peak systolic pressure to the next start of diastolic pressure (τ) and is affected by the pre- and afterloads (3, 13, 14, 29).

Noninvasive Doppler-derived myocardial performance index in rats with myocardial infarction: validation and correlation by conductance catheter. Am J Physiol Heart Circ Physiol 290: H1540–H1548, 2006. First published November 18, 2005; doi:10.1152/ajpheart.00935.2005—The rodent model of myocardial infarction (MI) is extensively used in heart failure studies. However, long-term follow-up of echocardiographic left ventricular (LV) function parameters such as the myocardial performance index (MPI) and its ratio with the fractional shortening (LVFS/MPI) has not been validated in conjunction with invasive indexes, such as those derived from the conductance catheter (CC). Sprague-Dawley rats with left anterior descending coronary artery ligation (MI group, n = 9) were compared with a sham-operated control group (n = 10) without MI. Transtracheal echocardiography (TTE) was performed every 2 wk over an 8-wk period, after which classic TTE parameters, especially MPI and LVFS/MPI, were compared with invasive indexes obtained by using a CC. Serial TTE data showed significant alterations in the majority of the noninvasive functional and structural parameters (classic and novel) studied in the presence of MI. Both MPI and LVFS/MPI significantly (P < 0.05 for all reported values) correlated with body weight (r = −0.58 and 0.76 for MPI and LVFS/MPI, respectively), preload recruitable stroke work (r = −0.61 and 0.63), LV end-diastolic pressure (LVEDP) (r = 0.82 and −0.80), end-diastolic volume (r = 0.61 and −0.58), and end-systolic volume (r = 0.46 and −0.48). Forward stepwise linear regression analysis revealed that, of all variables tested, LVEDP was the only independent determinant of MPI (r = 0.84) and LVFS/MPI (r = 0.83). We conclude that MPI and LVFS/MPI correlate strongly and better than the classic noninvasive TTE parameters with established, invasively assessed indexes of contractility, preload, and volumetry. These findings support the use of these two new noninvasive indexes for long-term analysis of the post-MI LV remodeling.

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possible interest of this parameter to capture the LV structural and functional alterations occurring during the post-MI remodeling period.

Also, because the LV fractional shortening (LVFS) is an ejection phase index (3), we hypothesized that the ratio of these two parameters (LVFS/MPI) would be more sensitive to MI-induced alterations of cardiac function as compared with MPI alone. Therefore, the aim of this study was to assess changes in MPI and the LVFS/MPI ratio in a rodent MI model and to correlate MPI as well as the related LVFS/MPI index to other invasive indexes obtained by CC.

MATERIALS AND METHODS

Animals. Male Sprague-Dawley rats were purchased from Charles River Breeding Laboratories (Lyon, France). They were maintained in temperature- and humidity-controlled rooms with typical light-dark cycle and given standard chow and tap water ad libitum. The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIM Publication No. 85-23, Revised 1996). The study design was approved by the Institutional Review Board and the University Hospital of Lausanne.

Experimental protocol. The rats in the MI group (n = 9) had a body weight of 254 ± 19 g (means ± SD) and were anesthetized with isoflurane (Forene; Abbott, Baar, Switzerland), intubated, and ventilated with 100% oxygen at 60 cycles/min with a tidal volume of 2 ml (model 683, Harvard Apparatus, Holliston, MA) before the surgical procedure was performed. The rats were placed on a heating pad to maintain body temperature, and disinfection was performed of the thorax. A left thoracotomy was performed at the third intercostal space to gain access to the heart. The pericardium was opened, and the left anterior descending coronary artery was located (between the left atrium and the pulmonary artery) and ligated with a 4.0 polypropylene suture (Ethicon, Somerville, NJ) to provoke the MI, which was visually confirmed by a change of color of the LV from red to a purplish-gray distal to the ligation site. The ribs were closed with two to three ligatures, a chest drain was inserted to avoid any pneumothorax, and the muscles surrounding the rib cage were sutured together before the skin was closed. Analgesia was given (Pro-Dafalgan) to attenuate any pain that ensued for the rodents because of the surgical procedure. The rats were then returned to the animal house once the anesthesia in the ventilating gas, and when they began to breathe spontaneously, the intubation tube was removed. The rats were then returned to the animal house once complete recovery was observed. A sham operation was performed on a similar control (CTRL) group (n = 10) with the rodents weighing 238 ± 7 g (means ± SD).

Invasive cardiac measurements with CC. Eight weeks after the initial operation, the rats were again anesthetized and intubated. The right neck region was disinfected to provide access to the carotid artery. The skin was opened, and the right jugular vein and carotid artery were isolated. A 2-Fr CC (SPR 838 Aria, Millar Instruments) was inserted into the left ventricle via the right carotid artery. Parallel artery were isolated. A 2-Fr CC (SPR 838 Aria, Millar Instruments) was inserted into the left ventricle via the right carotid artery. The skin was opened, and the right jugular vein and carotid artery were isolated. A 2-Fr CC (SPR 838 Aria, Millar Instruments) was inserted into the left ventricle via the right carotid artery. The skin was opened, and the right jugular vein and carotid artery were isolated. A 2-Fr CC (SPR 838 Aria, Millar Instruments) was inserted into the left ventricle via the right carotid artery.

Echocardiographic measurements. TTE was performed at baseline and every 2 wk for an 8-wk period with the use of a commercially available echocardiographic system (C250; Philips, Andover, MA) with an 18-MHz transducer (Acuson, Mountain View, CA) with the animal in the left lateral decubitus position. Light anesthesia was used during the analysis with isoflurane (Abbott) ventilated inside a nose cone at 0.5 l/min with 100% oxygen. Once asleep, the rat was shaven with an electrical razor (surgical clipper 9661, 3M Health Care). Ultrasound transonic blue gel (Tyco, Mirandola, Italy) was placed on the thorax to optimize visibility of the cardiac chambers. A 15-MHz linear array transducer (15L8) was used with a frame rate of 100 Hz by using bidimensional and color Doppler imaging. The probe was placed to obtain short- and long-axis and four-chamber views. From the long-axis view, an M-mode trace of the LV was obtained, and LV end-diastolic diameter (LVDed), LV end-systolic diameter (LVEDD), and posterior and septal wall diastolic wall thickness (PWth, and SWth) were measured. LVFS was calculated as follows: LVFS = (LVDed − LVEDD)/LVDed × 100. EF was calculated from a long-axis view by using planimetry as follows: EF (%) = 100 × (LVEDD − LVIIV)3/LVIV3. ET was calculated by using the following formula: ET = (LVEDD − LVIV)/ET × LVDed. The subscript I refers to data assessed with echocardiography. EDVn and ESVn were calculated by using Simpson’s method, and SVn was calculated as EDVn − ESVn. Aortic flow or cardiac output (CO) was recorded and calculated by using pulse Doppler imaging, with the smallest possible sample volume placed at the level of the aortic annulus. Doppler yields the velocity profile (aortic velocity time integral), which is multiplied with the cross-sectional area of the outflow tract to obtain flow. Integration of the velocity profile yields the aortic velocity time integral, which is obtained by multiplying the cross-sectional area of the aortic annulus with the time from the beginning to the end of the aortic flow wave (Fig. 1). IRT was measured as the interval between the aortic valve closure and the start of mitral flow, whereas ICT was obtained as the time delay between the cessation of mitral inflow and the onset of aortic ejection. Additionally, the mitral valve closure time (MCO) was measured. MPI is then defined as (MCO − ICT)/ET (Fig. 1). A new index of LV function, proposed by Broberg et al. (3), LVFS/MPI, was also assessed (3).

Statistical analysis. TTE was performed three times on each rat, and the measurements were averaged. Values are reported as means ± SD. Echocardiographic follow-up data were analyzed by using a general linear model of repeated-measurements ANOVA, with time as the within-subjects factor and group (MI or CTRL) as the between-subjects factor. At each instant in time, values were considered different between groups if statistical significance reached P < 0.05. If the ANOVA test indicated an effect of time within one of the groups, paired t-tests were performed, with baseline data as fixed control. P values < 0.05 were considered significant. The MPI and
LVFS/MPI were correlated with TTE and the CC measurements of LV systolic and diastolic function by using a Pearson product moment correlation, inasmuch as data were normally distributed, with relations considered significant when reaching $P < 0.05$. Correlations were performed with the pooled data and then with the two groups separated. Forward stepwise regression analysis was performed for MPI and LVFS/MPI (dependent variable) with all aforementioned CC- and TTE-derived parameters as independent variables. All analysis was done with SPSS software (SPSS 11.5, SPSS, Chicago, IL). A Bland-Altman analysis was performed between the CC and TTE data for SV, ESV, EDV, EF, and MPI by using the data measured at week 8 to compare the compatibility in ventricular volumes as measured by the noninvasive (TTE) and invasive (CC) techniques.

RESULTS

Hemodynamics assessed with CC (volumetric data with subscript c). ESVc and EDVc rose significantly in the MI group as compared with the CTRL group. V0 also increased significantly. The evolution of the heart failure caused the LVEDP to rise significantly (Table 1).

The $dP/dt_{\text{max}}$, $dP/dt_{\text{max}}$-EDVc, contractility index, and contraction time were all altered in the MI group. The slope of the ESPVR, $E_{\text{es}}$, was similar in both groups, though the ESPVR in

Table 1. Comparison between CTRL and MI groups for different invasive indexes analyzed with CC after euthanasia

<table>
<thead>
<tr>
<th>Parameters</th>
<th>CTRL Group</th>
<th>MI Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV pressures and volumes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDVc, ml</td>
<td>0.52±0.10</td>
<td>0.75±0.15*</td>
</tr>
<tr>
<td>ESVc, ml</td>
<td>0.15±0.07</td>
<td>0.56±0.14*</td>
</tr>
<tr>
<td>SVc, ml</td>
<td>0.35±0.07</td>
<td>0.25±0.05</td>
</tr>
<tr>
<td>V0, ml</td>
<td>0.155±0.039</td>
<td>0.254±0.092*</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>90±20</td>
<td>93±16</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>57±2.1</td>
<td>9.8±1.9†</td>
</tr>
<tr>
<td>LVSDP, mmHg</td>
<td>6.4±14.2</td>
<td>8.6±4.9</td>
</tr>
<tr>
<td>Isovolumic contraction phase indexes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$dP/dt_{\text{max}}$, mmHg/ms</td>
<td>5.128±1.241</td>
<td>4.606±1.407</td>
</tr>
<tr>
<td>$dP/dt_{\text{max}} - EDVc$, mmHg s⁻¹ μl⁻¹</td>
<td>25.8±11.2</td>
<td>20.5±7.0*</td>
</tr>
<tr>
<td>CI, s⁻¹</td>
<td>95.7±6.7</td>
<td>76.3±11.6*</td>
</tr>
<tr>
<td>ICT, ms</td>
<td>17.6±2.4</td>
<td>20.2±1.8*</td>
</tr>
<tr>
<td>Ejection phase indexes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_{\text{es}}$, %</td>
<td>54.2±15.4</td>
<td>36.1±14.3*</td>
</tr>
<tr>
<td>$CO_c$, ml/min</td>
<td>108±45</td>
<td>72±33*</td>
</tr>
<tr>
<td>Active phase of relaxation indexes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\tau$, ms</td>
<td>12.2±11.3</td>
<td>17.3±6.8*</td>
</tr>
<tr>
<td>$dP/dt_{\text{max}}$, mmHg/ms</td>
<td>-4.722±475</td>
<td>-4.406±1200</td>
</tr>
<tr>
<td>IRT, ms</td>
<td>46.4±4.7</td>
<td>53.6±5.1*</td>
</tr>
</tbody>
</table>

Values are means ± SD. CTRL, control; MI, myocardial infarction; CC, conductance catheter; LV, left ventricular; EDVc, end-diastolic volume; ESVc, end-systolic volume; SVc, stroke volume; $E_{\text{es}}$, ejection fraction; $CO_c$, cardiac output (subscript c refers to data measured with CC); V0, volume axis intercept of end-systolic pressure-volume relationship; LVEDP, LV end-diastolic pressure; LVSDP, LV start of diastolic pressure; $dP/dt_{\text{max}}$, peak positive value of time derivative of LV pressure; CI, contractility index; ICT, isovolumetric contraction time; $E_{\text{es}}$, LV mass, end-systolic elastance normalized to LV mass; PRSW, preload recruitable stroke work; $\tau$, time constant of relaxation derived from peak systolic pressure to next beginning of diastolic pressure; IRT, isovolumic relaxation time. *$P < 0.05$, †$P < 0.01$ CTRL vs. MI at same age.
the MI group did shift notably to the right, thus raising the $V_0$ values. However, $E_{es}$ normalized to LV mass decreased in the MI group. Also, the PRSW and $SV_e$ were compromised in the MI group. EFc and COc decreased significantly in the MI group (Table 1). The $\tau$ increased in the MI group. The IRT was significantly prolonged in the MI group. The $dP/dt_{min}$ was augmented by 10% in the MI group ($P = \text{not significant; Table 1}$.)

Echocardiography (volumetric data with subscript e) and serial follow-up data. Body weight increased with age in both groups but remained significantly lower in the MI group (Fig. 2A). LV mass increased with age in both groups; however, after 8 wk, absolute LV mass was higher in the MI group (0.98 $\pm$ 0.11 g CTRL vs. 1.29 $\pm$ 0.10 g MI; $P < 0.01$). The same applied for the LV weight-to-body weight ratio (1.70 $\pm$ 0.20 g/kg CTRL vs. 2.45 $\pm$ 0.45 g/kg MI; $P < 0.01$). The heart rate was comparable between the CTRL and MI groups (318 $\pm$ 29 and 319 $\pm$ 29 beats/min, respectively) at week 8.

The EF, was comparable at baseline but decreased significantly in the MI group (Fig. 2H). The EDVe and ESVe were significantly greater in the MI group versus the CTRL group (Fig. 2B and C). The SVe decreased significantly in the MI group (Fig. 2D).

RWT and LVFS attenuated in the MI group but remained stable in the CTRL group (Fig. 2, E and F). $V_{cf}$ rose slightly in the CTRL group but was conserved in the MI group (Fig. 2G). COc was significantly less in the MI group ($P < 0.05$) at week 8 (89 $\pm$ 14 ml/min MI vs. 112 $\pm$ 20 ml/min CTRL).

$\text{MPI and valve opening and closure timing parameters.}$ The ICT was stable in the CTRL group but was prolonged in the MI group. The IRT was not different between groups but did rise in the MI group when compared with baseline at weeks 6 and 8 ($P < 0.001$). ET remained stable over time without any relevant difference between the groups. Consequently, the MI group increased significantly in the MI group when compared with the CTRL group (Fig. 2I). LVFS/MPI decreased significantly in the MI group as compared with the CTRL group (Fig. 2J).

Correlation of invasive parameters versus $\text{MPI and LVFS}$/$\text{MPI (pooled data).}$ In the univariate correlation analysis, both MPI and LVFS/MPI were significantly correlated with body weight, LVEDP, PRSW, EDV, and ESV (Table 2).

Forward stepwise linear regression analysis revealed that, of all the independent variables tested, LVEDP was the only independent determinant of MPI ($R^2 = 0.70, P < 0.0001$) and of LVFS/MPI ($R^2 = 0.68, P < 0.0001$).

Correlation of invasive parameters versus $\text{MPI and LVFS}$/$\text{MPI (groups separated).}$ From the above pooled data, the two groups were separated and univariate regression analysis was applied. The corresponding graphs, with the linear regressions and correlation coefficients, are shown in Fig. 3. For the majority of the parameters, the regression lines of the pooled data and of the separated groups are almost identical or similar. Overall, the correlation coefficients based on the pooled data were comparable to those derived from the separate groups (Fig. 3 and Table 2).

Invasive versus noninvasive assessment of ventricular volume, MPI, and EF (Bland-Altman analysis). The average differences found were as follows: for EDV, 0.03 $\pm$ 0.05 ml (Fig. 4A); for ESV, $-0.04 \pm 0.03$ ml (Fig. 4B); for SV, $0.003 \pm 0.02$ ml (Fig. 4C); for EF, $5.8 \pm 5.4\%$ (Fig. 4D); and for MPI, $0.007 \pm 0.02$ (Fig. 4E). The correlation coefficients for ESV, EDV, SV, EF, and MPI when absolute values were compared between TTE and CC were found to be 0.92, 0.98, 0.92, 0.95, and 0.85, respectively (all $P < 0.05$). The mean $\alpha$ value used for the volume correction was 2.5 $\pm$ 0.8.

Intra- and interobserver variability. Intra- and interobserver differences were 5.1 $\pm$ 2.1% and 4.4 $\pm$ 7.7% for LVFS, 6.5 $\pm$ 5.8% and 5.8 $\pm$ 7.7% for EF, 6.8 $\pm$ 3.6% and 6.8 $\pm$ 8.8% for $V_{cf}$, and 9.6 $\pm$ 1.9% and 7.0 $\pm$ 5.0% for MPI, respectively.

DISCUSSION

We evaluated the adaptation response and long-term effects of MI on cardiac function using TTE in rodents and after 8 wk compared these data with invasively measured indexes of ventricular function. A number of classic and newly proposed parameters (MPI and LVFS/MPI) derived noninvasively from TTE were computed and reported. These changes post-MI were profound and easily detectable by the different noninvasive indexes, including the two newly proposed indexes. Moreover, significant correlations were established between the new and classic noninvasive and established invasive parameters (PRSW, LVEDP, EDV, and ESV) of ventricular function. The best and most significant correlation coefficients were established between the two new parameters and PRSW and LVEDP. EDV expressed similar correlation coefficients compared with the classic TTE parameters, whereas ESV showed the lowest correlation; however, the ESV correlation was still significant. Therefore, MPI and LVFS/MPI reflect well the changes post-MI in contractility (PRSW), preload (LVEDP), and volume (EDV and ESV).

Serial assessment of cardiac function. Classically, EF, RWT, LVFS, and $V_{cf}$ are used to evaluate systolic function with TTE in rat models of pressure and volume overload (4, 10, 26). In a rodent study with MI by Sjaastad et al. (24), body weight, LVFS, $V_{cf}$, and CO were all compromised because of the MI. Gao et al. (9) performed TTE in mice, demonstrating that the LVFS remains constant over time in control mice but attenuates with time in a model of MI. In our study, all of the above parameters and MPI and LVFS/MPI were significantly compromised over time because of the MI. Slama et al. (26) and Salemi et al. (23) have reported the MPI in conjunction with serial studies, but only in hypertensive models. RWT is only useful in studies measuring myocardial wall adaptations due to hypertensive response (10). If used in MI models with an apical infarction present, but M-mode measured at the papillary muscle level, values will be falsely positive because the MI would cause wall thinning at the apex. However, in our study, all MIs were anteroapical, precluding this phenomenon. Therefore, the MPI, and recently LVFS/MPI (3), were introduced because they have been reported to be independent of load and LV geometry (3, 29). Slama et al. (26) and Salemi et al. (23) have reported the MPI in conjunction with serial studies, but only in hypertensive models. In our study, these two novel parameters fare well compared with the classic TTE parameters reported earlier and visible in Fig. 2. Moreover, the LVFS/MPI seems to visually express alterations in cardiac function post-MI more clearly, compared with the classic parameters, despite the large standard deviations (Fig. 2J).
Fig. 2. Echocardiographic measurements from baseline (BL) to week (W) 8 (W8) (■, MI; □, CTRL). A: body weight. B: end-diastolic volume (EDVe). Subscript e denotes echocardiographic data. C: end-systolic volume (ESVe). D: stroke volume (SVe). E: relative wall thickness. F: LV fractional shortening (LVFS; in %). G: velocity of circumferential fiber shortening (Vcf in s⁻¹). H: ejection fraction (EF in %). I: MPI. J: LVFS/MPI. Statistical significance expressed as *P < 0.05 and **P < 0.001.
Fig. 3. Correlation coefficients ($R^2$) of conductance catheter (CC) parameters vs. MPI and LVFS/MPI for the CTRL (○) and MI (●) groups using univariate regression analysis. See Fig. 2 and Table I for abbreviations.
Table 2. Correlation coefficients and statistical significance of MPI, LVFS/MPI, LVFS, EF, V<sub>cf</sub>, and RWT vs. CC parameters for the combined groups using univariate regression analysis

<table>
<thead>
<tr>
<th>TTE Parameters</th>
<th>MPI</th>
<th>LVFS/MPI</th>
<th>LVFS</th>
<th>EF</th>
<th>V&lt;sub&gt;cf&lt;/sub&gt;</th>
<th>RWT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>0.58†</td>
<td>0.76†</td>
<td>0.82†</td>
<td>0.79†</td>
<td>0.86†</td>
<td>0.54*</td>
</tr>
<tr>
<td>PRSW</td>
<td>0.61†</td>
<td>0.63†</td>
<td>0.54*</td>
<td>0.58*</td>
<td>0.58*</td>
<td>0.58*</td>
</tr>
<tr>
<td>LVEDP</td>
<td>0.82†</td>
<td>-0.80†</td>
<td>-0.68†</td>
<td>-0.67*</td>
<td>-0.46*</td>
<td>-0.78†</td>
</tr>
<tr>
<td>EDV</td>
<td>0.61†</td>
<td>-0.58†</td>
<td>-0.55*</td>
<td>-0.64*</td>
<td>-0.70†</td>
<td>-0.76†</td>
</tr>
<tr>
<td>ESV</td>
<td>0.46*</td>
<td>-0.48*</td>
<td>-0.58*</td>
<td>-0.78†</td>
<td>-0.70†</td>
<td>-0.76†</td>
</tr>
</tbody>
</table>

MPI, myocardial performance index; LVFS, LV fractional shortening; V<sub>cf</sub>, velocity of circumferential fiber shortening; RWT, relative wall thickness; TTE, transthoracic echocardiography. *P < 0.05; †P < 0.01.
These deviations are a result of the fact that the infarct size in the MI model is difficult to homogenize and varies between 37 ± 7%, not forgetting the variations of intra- and interobserver variability. Also, it should be acknowledged that MPI is highly dependent on timing intervals and temporal resolution and hence susceptible to interpretation errors in cases when heart rate changes over time during the experimental procedure.

**Noninvasive versus invasive assessment of cardiac function.**

We measured cardiac function using both TTE and CC in the same animal, allowing us to correlate findings from both techniques. Hence, the relation between classic (EF, LVFS, \( V_{cf} \), and RWT) and novel indexes such as MPI and LVFS/MPI and established invasive cardiac function parameters could be derived (Table 2). The MPI and LVFS/MPI express the largest correlation coefficients and most significant for PRSW and LVEDP compared with the classic indexes. Similar coefficient values are found between classic and novel indexes with respect to EDV. However, ESV shows the smallest relationship for the novel indexes; nonetheless, it is still significantly comparable. LVFS correlated well to the invasive indexes but not as well as MPI and LVFS/MPI (Table 2). LVFS has also been shown to be related to \( dP/dt_{max} \) (and is modified with contractility and afterload manipulations) (3, 16) and \( dP/dt_{min} \) (9). Therefore, LVFS could be considered as a good marker to represent serial and end point cardiac function. However, \( V_{cf} \) has been shown to be dependent on \( dP/dt_{max} \) and is modified with contractility and preload and afterload manipulations (3).

In our study, \( V_{cf} \) could not correlate to invasive indexes except for LVEDP.

With regard to the MPI, it has been reported that the MPI correlates with \( dP/dt_{max} \), \( dP/dt_{min} \), LVEDP, and \( \tau \) and that it is dependent on contractility yet also affected by preload and afterload (3, 14, 25). The dependence of MPI on preload was also reported by Moller et al. (13) in patients without MI. However, in a recent publication by Cheung et al. (6), this phenomenon could not be reproduced in a porcine model. In our study, MPI correlated with PRSW, a measure of contractility, and with LVEDP and LV volumes. Tei et al. (29) also found correlations of MPI with \( dP/dt_{max} \) and \( \tau \) when using cardiac catheterization in larger mammals, but we could not confirm this finding using our data. In an acute MI setting, Morgan et al. (14) also showed the MPI to correlate to end-systolic and end-diastolic TTE dimensional values. We advocate this by expressing a relationship between MPI, ESV, and EDV (Table 2). Furthermore, it must be stipulated that the MPI is LV geometry independent and thus ideal for studying the course of a disease associated with chamber remodeling, which is typically elaborated during MI (29).

With regard to the LVFS/MPI, it was shown by Broberg et al. (3) that this ratio correlated strongly with \( dP/dt_{max} \) in mice and was dependent on contractility and afterload variations but not on preload variations. However, in our study, the above ratio correlated to the load-independent contractile parameter PRSW, to LVEDP (preload), and to volumetric parameters (Table 2) but not to \( dP/dt_{max} \). Therefore, the ratio is also affected by preload because LVEDP varies with MI. In our study of chronic MI, LVFS/MPI was the most sensitive to changes in contractility (PRSW) and filling (LVEDP) compared with classic TTE parameters. In multiple linear regression analysis, LVEDP appeared as the strongest predictor of MPI and LVFS/MPI, suggesting that these indexes are potentially useful noninvasive indicators of filling pressure in the rat, at least in the setting of cardiac remodeling after MI.

It is to be emphasized that the reported data were obtained in a pooled analysis, including both CTRL and MI data. When comparing EDV, ESV, EF, MPI, and SV as assessed by CC with TTE by using the Bland-Altman analysis, the mean difference is close to zero for all parameters validating the coherence of the two methods. Slight discrepancies exist between the two methods because the TTE accuracy is frame rate dependent and the CC accuracy depends on initial calibration, \( \alpha \) estimation, and the calculation of parallel conductance (8). With this in mind, both methods are representative and suitable for evaluating changes in cardiac function. EFc correlates well to EF (6) and EFc (9; \( r = 0.80 \) with \( P < 0.01 \)), and the differences in EF that are visible between the two groups are similar between the two methods (bias 6%), as seen in Table 1 and Fig. 4, respectively. Similar correlations between CC and TTE have been demonstrated, such as those we found for ESV and EDV (5). Also, MPIc has been correlated to MPIc with a bias of only 0.007 (roughly 2%). Because of the fact that at week 8, acceptable concordance was achieved between methods, one can assume that during the time course of the study, similar relations can be established, thus validating not just the end points but also the cardiac structural (EDV, ESV, and SV) and functional (EF and MPI) variations from the baseline of the study.

**Study limitations.** The number of animals in each of the subgroups was comparable to other studies, justifying detailed analysis of the MPI and LVFS/MPI within each subgroup. When compared with other research groups, between 6 and 12 rats are used per group (7, 9, 26) and all correlations are performed by pooling the analyzed data (14, 25). Therefore, after a detailed literature review, no other group has demonstrated acceptable correlations by using subgroup analysis techniques. Another limitation arises from the use of anesthetics that might influence the data because of their effect on inotropy and chronotropy. However, following previous reports, we used isoflurane during the complete study period because it seems to be the most appropriate technique for repeated and prolonged studies necessitating stable hemodynamic conditions (21). In addition, the simultaneous measurement of the TTE and CC parameters is technically challenging because the rat is small and the positioning of the TTE probe is performed with the animal in the lateral decubitus position.

In conclusion, we were able to follow serial changes in cardiac function post-MI with these novel parameters (MPI or LVFS/MPI) with success and as efficiently as with classic TTE parameters. Moreover, LVFS/MPI visually expressed better the serial modifications in cardiac function. Both novel parameters were correlated to the load-independent contractile parameter PRSW and to the preload parameter LVEDP, which was pertinent in following preload changes post-MI. Finally, chamber remodeling post-MI can successfully be followed because of the fact that ESV and EDV both correlate to MPI and LVFS/MPI.

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