Assessing left ventricular systolic dysfunction after myocardial infarction: are ejection fraction and dP/d\(t_{\text{max}}\) complementary or redundant?

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Assessing left ventricular systolic dysfunction after myocardial infarction: are ejection fraction and dP/d\(t_{\text{max}}\) complementary or redundant? *Am J Physiol Heart Circ Physiol* 302: H1423–H1428, 2012. First published February 3, 2011; doi:10.1152/ajpheart.01211.2011. — Among the various cardiac contractility parameters, left ventricular (LV) ejection fraction (EF) and maximum dP/dt (dP/d\(t_{\text{max}}\)) are the simplest and most used. However, these parameters are often reported together, and it is not clear if they are complementary or redundant. We sought to compare the discriminative value of EF and dP/d\(t_{\text{max}}\) in assessing systolic dysfunction after myocardial infarction (MI) in swine. A total of 220 measurements were obtained. All measurements included LV volumes and EF analysis by left ventriculography, invasive ventricular pressure tracings, and echocardiography. Baseline measurements were performed in 132 pigs, and 88 measurements were obtained at different time points after MI creation. Receiver operator characteristic (ROC) curves to distinguish the presence or absence of an MI revealed a good predictive value for EF [area under the curve (AUC) of 0.998] but not by dP/d\(t_{\text{max}}\) (AUC: 0.69, P < 0.001 vs. EF). Dividing dP/d\(t_{\text{max}}\) by LV end-diastolic pressure and heart rate (HR) significantly increased the AUC to 0.87 (P < 0.001 vs. EF). In naive pigs, the coefficient of variation of dP/d\(t_{\text{max}}\) was twice than that of EF (22.5% vs. 9.5%, respectively). Furthermore, in \(n = 19\) pigs, dP/d\(t_{\text{max}}\) increased after MI. However, echocardiographic strain analysis of 23 pigs with EF ranging only from 36% to 40% after MI revealed significant correlations between dP/d\(t_{\text{max}}\) and strain parameters in the noninfarcted area (circumferential strain: r = 0.42, P = 0.05; radial strain: r = 0.71, P < 0.001). In conclusion, EF is a more accurate measure of systolic contractility than dP/d\(t_{\text{max}}\) in a swine model of MI. Despite the variability of dP/d\(t_{\text{max}}\) both in naïve pigs and after MI, it may sensitively reflect the small changes of myocardial contractility.

METHODS

Animal model. The experimental protocols complied with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and standards of United States regulatory agencies. They were approved by the Institutional Animal Care and Use Committee of the Mount Sinai School of Medicine. All animals underwent hemodynamic and volume measurements before any interventions that may affect these parameters. All animals that received treatments to specifically influence cardiac function before the measurements were excluded from the study. Yorkshire pigs were premedicated using intramuscular Telazol (8.0 mg/kg, Fort Dodge, IA). After the placement of an intravenous injection line, animals were intubated and ventilated with 100% O\(_2\). Pigs were positioned in dorsal recumbency, and general anesthesia was maintained with intravenous Propofol (6–8 mg·kg\(^{-1}\)·h\(^{-1}\)) throughout the procedure. Electrocardiograms and pulse oximeter measurements were recorded at 5-min intervals. Continuous monitoring with an intravenous saline infusion was maintained for a period of 30 min to stabilize the hemodynamic status. A transhilar echocardiographic examination was performed to exclude major structural heart diseases.

Pressure measurements. Under sterile conditions, a percutaneous puncture provided arterial access and allowed sheath placement. After sheath insertion, heparin (100 IU/kg iv) was administered to maintain an activated coagulation time of 250–300 s. Through the femoral arterial sheath, a Millar catheter (Millar Instruments, Houston, TX) was advanced to the LV to measure the following hemodynamic parameters: LV maximum pressure, LV end-diastolic pressure (EDP), dP/d\(t_{\text{max}}\) and HR. MPVS Ultra (Millar Instruments) was used to acquire analog data and convert it to digital data. Data analysis was performed using iox2 (Emka Systems, West Sacramento, CA).
Technologies, Falls Church, VA). All measurements were performed after the confirmation of hemodynamic stability for 3 min. An average of two respiratory cycles was used for the analysis of each parameter.

**Volume measurements.** Immediately after the pressure measurements, left ventriculography was performed using a contrast agent injected at a high rate. Clear delineation of the ventricular border enabled an automatic trace of the ventricular cavity. Electrodes of the Millar catheter placed 7 mm apart were used for the calibration of the length of the LV measured on the ventriculographic image. End-diastolic volume (EDV) and end-systolic volume (ESV) were calculated from left ventriculography by the area-length method (30). Stroke volume (SV) was calculated EDV – ESV, and EF was calculated as SV/EDV. Body surface area (in m²) was calculated (16) from left ventriculography by the area-length method (30).

MI creation. The creation of the MI has been described in detail elsewhere (12). Briefly, after cardiac performance was evaluated in naïve pigs, a bolus of Amiodarone (1 mg/kg) was given intravenously over 10 min, followed by a continuous infusion at the rate of 1 mg/min for the duration of the procedure. A 7-Fr hockey-stick catheter (Cordis, Miami, FL) was advanced to the left coronary artery, and a 0.014-in. guide wire (Abbott, Park, IL) was advanced into the left anterior descending artery. An 8-mm-long, 4.0-mm VOYAGER over-the-wire balloon (Abbott) was advanced beyond the first branch. The balloon was then inflated to 3 atm for 90–120 min, followed by an embolic coil implantation in some of the animals (n = 19). The remaining animals were reperfused without a coil. After the confirmation of hemodynamic stability, animals were allowed to recover, housed in their cages, and examined daily for any signs of pain or distress.

**Echocardiographic strain measurements.** A Philips iE-33 ultrasound system (Philips Medical Systems, Andover, MA) was used to acquire echocardiographic data with a multifrequency imaging transducer. Two-dimensional (2-D) cross-sectional images of the parasternal short axis of the LV were obtained at the level of the papillary muscle, with a high frame rate. Data spanning at least three consecutive heartbeats were acquired and stored as digital images. The 2-D images were loaded into the Q-lab application (Philips Medical Systems) for strain analysis using a speckle-tracking algorithm. The LV was divided into six segments and categorized into three zones: infarct, border, and remote areas. Circumferential and radial strains were analyzed for each area.

**Statistical analysis.** Data are expressed as means ± SE except in Fig. 4, where means ± SD are shown. The coefficient of variation was calculated by dividing the SD by the mean. Pearson’s correlation and linear regression were used to examine the direction and strength of the relationships between the study variables, and corresponding scatterplots were generated. Receiver operating characteristic (ROC) curves were constructed to assess the ability of various parameters to determine the presence of MI, and the area under the ROC curve (AUC) was calculated. Comparisons of AUCs were performed using the nonparametric approach. A paired t-test was used to compare preinfarct (naïve) and post-MI measurements taken serially on animals at each time point. Relative changes of EF and dP/dt max before and after MI were obtained in animals with MI. A Bland-Altman plot of the difference between relative post-MI EF change and relative post-MI dP/dt max change (y-axis) against their average (x-axis) was used to measure agreement between the

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**Table 1. LV size and function before and after myocardial infarction**

<table>
<thead>
<tr>
<th></th>
<th>Naïve</th>
<th>2 days</th>
<th>7 days</th>
<th>1 mo</th>
<th>3 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of measurements</strong></td>
<td>132</td>
<td>8</td>
<td>23</td>
<td>48</td>
<td>9</td>
</tr>
<tr>
<td><strong>Ejection fraction, %</strong></td>
<td>70.5 ± 0.6</td>
<td>38.4 ± 2.1*</td>
<td>40.1 ± 1.3*</td>
<td>37.0 ± 1.2*</td>
<td>36.3 ± 3.1*</td>
</tr>
<tr>
<td><strong>Maximum dP/dt, mmHg/s</strong></td>
<td>2020 ± 39</td>
<td>1817 ± 113*</td>
<td>2006 ± 109</td>
<td>1567 ± 49*</td>
<td>1605 ± 65*</td>
</tr>
<tr>
<td><strong>Maximum LV pressure, mmHg</strong></td>
<td>106 ± 1.4</td>
<td>96 ± 2.7</td>
<td>106 ± 3*</td>
<td>114 ± 2*</td>
<td>124 ± 3.7</td>
</tr>
<tr>
<td><strong>End-diastolic pressure, mmHg</strong></td>
<td>14.1 ± 0.4</td>
<td>20.2 ± 2.3*</td>
<td>22.0 ± 1.8*</td>
<td>25.8 ± 1.2*</td>
<td>19.2 ± 2.3</td>
</tr>
<tr>
<td><strong>Body weight, kg</strong></td>
<td>19.2 ± 0.1</td>
<td>20.3 ± 0.4</td>
<td>20.5 ± 0.2*</td>
<td>24.8 ± 0.2*</td>
<td>38.2 ± 1.3*</td>
</tr>
<tr>
<td><strong>Heart rate, beats/min</strong></td>
<td>75 ± 2</td>
<td>111 ± 10*</td>
<td>98 ± 4*</td>
<td>70 ± 3</td>
<td>74 ± 4</td>
</tr>
<tr>
<td><strong>EDV, ml</strong></td>
<td>38.1 ± 0.5</td>
<td>49.5 ± 1.9</td>
<td>59.2 ± 2.0*</td>
<td>81.8 ± 2.5*</td>
<td>109.9 ± 7.3*</td>
</tr>
<tr>
<td><strong>EDV index, ml/m²</strong></td>
<td>74.9 ± 1.0</td>
<td>93.6 ± 3.3</td>
<td>111.4 ± 3.7*</td>
<td>135.5 ± 4.1*</td>
<td>138.0 ± 9.7*</td>
</tr>
<tr>
<td><strong>ESV, ml</strong></td>
<td>11.2 ± 0.3</td>
<td>30.4 ± 1.4*</td>
<td>35.8 ± 1.6*</td>
<td>52.5 ± 2.5*</td>
<td>70.9 ± 6.8*</td>
</tr>
<tr>
<td><strong>ESV index, ml/m²</strong></td>
<td>22.1 ± 0.6</td>
<td>57.4 ± 2.4*</td>
<td>67.4 ± 3.1*</td>
<td>87.1 ± 4.1*</td>
<td>89.5 ± 9.2*</td>
</tr>
<tr>
<td><strong>SV, ml</strong></td>
<td>26.8 ± 0.4</td>
<td>19.1 ± 1.4*</td>
<td>23.4 ± 0.9</td>
<td>29.2 ± 0.7</td>
<td>38.8 ± 3.0*</td>
</tr>
<tr>
<td><strong>SV index, ml/m²</strong></td>
<td>52.5 ± 0.8</td>
<td>36.1 ± 2.6*</td>
<td>43.9 ± 1.7*</td>
<td>48.4 ± 1.1*</td>
<td>48.3 ± 3.1*</td>
</tr>
</tbody>
</table>

Values are means ± SE. LV, left ventricular; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume. *P < 0.05 vs. baseline naïve measurements (by paired t-test).
two parameters in detecting post-MI change. *P* values below 0.05 were considered statistically significant.

**RESULTS**

A total of 220 measurements were obtained. Baseline measurements (naïve animals) before any intervention were performed in 132 pigs, and all the pigs underwent MI creation subsequently. Eighty-eight measurements from pigs that survived after MI creation and did not receive any treatment to specifically influence cardiac function were assigned to post-MI measurements. Multiple post-MI measurements were performed in nine pigs at different time points. LV pressure and volume data at each time points are shown in Table 1. Detection of MI. ROC curves for various parameters were generated to compare their ability to detect MI. AUCs for EF and dP/dt\(_{\text{max}}\) to identify pigs with MI were 0.998 and 0.69 (\(P < 0.001\)), respectively (Fig. 1A). The ROC curves for volume parameters are shown in Fig. 1B. Both the ESV index and EDV index appeared to be excellent predicting factors for detecting MI, and AUCs were 0.998 and 0.98, respectively. However, the AUC of the SV index remained small (0.70) compared with that of the ESV index (\(P < 0.001\)) and EDV index (\(P < 0.001\)). The ratio of dP/dt\(_{\text{max}}\) over EDP significantly increased the AUC compared with that of dP/dt\(_{\text{max}}\) alone (\(P < 0.001\)). Further adjustment through division by HR was also associated with an increased AUC without outperforming the adjustment on EDP (\(P < 0.001\)) vs. dP/dt\(_{\text{max}}\) alone and \(P = 0.13\) vs. dP/dt\(_{\text{max}}/\text{EDP}\); Fig. 2). The AUC for dP/dt\(_{\text{max}}\) adjusted on EDP or adjusted on EDP and HR remained significantly lower than the AUC for EF (\(P < 0.001\)).

**Correlation of EF and dP/dt\(_{\text{max}}\) and their distribution.** A scatterplot of EF versus dP/dt\(_{\text{max}}\) is shown in Fig. 3A. Only a weak correlation was found between EF and dP/dt\(_{\text{max}}\) (Fig. 3A). A Bland-Altman plot was used to assess the agreement of EF and dP/dt\(_{\text{max}}\) in measuring the deterioration of LV function after MI (Fig. 5B). It revealed better agreement when the relative deterioration (measured as the average of relative deterioration of both parameters) was large; however, EF showed higher sensitivity to MI (higher EF relative deterioration) when the average relative deterioration was small.

**Relative change before and after MI.** There was no statistically significant correlation between the deterioration of EF and the deterioration of dP/dt\(_{\text{max}}\), caused by MI, measured as relative changes of EF and dP/dt\(_{\text{max}}\) associated with MI (\(r = 0.21, P = 0.06\); Fig. 5A). A Bland-Altman plot was used to assess the agreement of EF and dP/dt\(_{\text{max}}\) in measuring the deterioration of LV function after MI (Fig. 5B). It revealed better agreement when the relative deterioration (measured as the average of relative deterioration of both parameters) was large; however, EF showed higher sensitivity to MI (higher EF relative deterioration) when the average relative deterioration was small.

**dP/dt\(_{\text{max}}\) and regional LV function.** To investigate whether the wide distribution of dP/dt\(_{\text{max}}\) change was partly due to increased contractility in the remote myocardium, echocardiographic strain analysis was performed in 23 pigs with MI. Pigs with an EF of 36 – 40% (mean ± 2SE of the entire MI pig group) were chosen so that the relation could be assessed in pigs with comparable EF. While no correlation was found between the strain values in the infarct area and dP/dt\(_{\text{max}}\), moderate correlation was found between both radial and cir-
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Fig. 4. Comparative variability of EF and dP/dt\textsubscript{max} in naïve pigs (n = 132). Values are means ± SD. The coefficient of variation of EF was 9.4%, and that of dP/dt\textsubscript{max} was 22.5%.

Not clear whether they are redundant or complementary, and whether one is more accurate than the other in the assessment of systolic dysfunction. In fact, limited information is available on the direct comparison of these parameters. To our knowledge, this is the first study that compared these widely used fundamental parameters in large numbers of animals with a clinically relevant ischemic heart failure model. Our results show EF to be more reliable than dP/dt\textsubscript{max} in detecting systolic dysfunction after MI. We thought that this superiority of EF over dP/dt\textsubscript{max} was due to the well-known preload dependence of dP/dt\textsubscript{max} (14, 26), and we compared EF to dP/dt\textsubscript{max} adjusted on EDP for that matter, showing improved accuracy of the adjusted parameter that, nonetheless, did not reach the accuracy of EF. In addition, the measurement of post-MI LV remodeling by the ESV index and EDV index appeared to have an excellent predictive value as well. In our study, we insisted on comparing and correlating non-overlapping parameters. Therefore, in contrast to EF and LV volume indexes, dP/dt\textsubscript{max} is derived from the LV pressure-time curve, and the preload adjustment of dP/dt\textsubscript{max} was done by dividing dP/dt\textsubscript{max} by EDP, independently of volume measurements.

The EF-dP/dt\textsubscript{max} Bland-Altman plot indicates that with more severe depression of cardiac function after MI, both EF and dP/dt\textsubscript{max} show a comparable relative decrease. However, when the cardiac function is less impaired, the relative decrease of dP/dt\textsubscript{max} is smaller compared with that of EF. One explanation is that dP/dt\textsubscript{max} decreases when there is a global ventricular systolic dysfunction (more likely in MI with very low EF) but can be compensated by the noninfarcted area when the functional impairment is limited. Significant correlation between dP/dt\textsubscript{max} and remote area regional function in pigs with nearly equal and reduced EF supports the latter hypothesis. Therefore, dP/dt\textsubscript{max} can be modulated bidirectionally, in a more sensitive way than measures of global functional impairment, such as EF. Together with the lack of connection with LV volume remodeling, this explains the low predictive value of dP/dt\textsubscript{max} for detecting MI.

Most studies that have used dP/dt\textsubscript{max}-related parameters had similar HRs between the animals (3, 15, 18), which makes the Treppe effect less likely to play a role (37). However, not all animals have equivalent HRs, which can also fluctuate with some of the treatment regimens. Furthermore, while dP/dt\textsubscript{max} is usually independent of afterload since it derives from the pressure change before the aortic valve opening, it is preload...
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The superiority of EF to dP/dt max is partly due to the fact that EF = SV/EDV and thus EF accounts for the preload, in contrast with the preload dependence of dP/dt max. This is supported by our results showing an improved accuracy of (dP/dt max)/EDP compared with dP/dt max alone in detecting MI and by the literature, where the slope of dP/dt max versus EDP is an accepted load-independent parameter of LV systolic function (8, 31, 37). Thus, the adjustment of dP/dt max, mostly with EDP, increased its predictive value for MI detection. Several other factors, such as longitudinal contraction (2), timing of aortic valve opening (39), and size of the LV (27), have a certain degree of influence on dP/dt max. In fact, in the present study, for naive animals with assumed normal and similar cardiac function, the coefficient of variation in dP/dt max was 22.5%, whereas that of EF was only 9.4%. Although we included only nondiseased animals of similar sizes (19 ± 2 kg) that were studied under identical anesthesia conditions, the twice higher variability of dP/dt max compared with EF is an additional drawback of this parameter, more sensitive to measured or unmeasured individual interanimal variation in experimental conditions, such as response to anesthetic drugs. In addition, as shown in Fig. 5A, some of the animals even showed increased dP/dt max after MI. Thus, this value may not be suitable for interanimal comparison or for the comparison of different time points in the identical animal. Instead, the sensitive response to various factors is an advantage for the assessment of small changes in contractility during continuous or consecutive measurements, where many of the factors remain consistent.

Our results demonstrated a moderate correlation between EF and (dP/dt max)/EDP/HR. This implies that EF is a parameter that integrates contractility, measured by pressure rise, and HR. Furthermore, as mentioned above, EF also reflects LV remodeling. Higher HR (6–7, 13) and larger size of the heart (11, 33, 38) are established predictors of poor outcomes in patients with systolic heart failure. As such, EF is a comprehensive parameter of various important factors closely related to the patients’ prognosis. This may explain why EF is a powerful predictor of the prognosis of the patients with heart failure. Further studies are needed to verify that the superiority of EF over dP/dt max in detecting myocardial infarction in our study translates in a superior clinical prognostic value for EF compared with dP/dt max in patients with heart failure or after MI. In the spirit of our study, it may also be possible to establish a complementary prognostic value for dP/dt max in situations where the predictive power of EF can be limited.

Limitations. Because of the time separating post-MI measurements from naive measurements, we cannot exclude the potential effect of animal growth. As the pigs grow, cardiac size increases and the ventricular volumes increase. This may be affecting the high predictive values obtained in volume parameters. To minimize the effect of growth, we used the volume indexes by dividing the volume with body surface area. In our experience, these indexes remain stable during the pigs’ growth for the duration of our study period. The adjustment of dP/dt max with HR and EDP by simply dividing this value may not be justified in some of the cases, since it does not always have linear relationships to HR and EDP. However, the higher correlation to EF and higher predictive value of MI after the division suggests that the influence of HR and EDP can be reduced by this adjustment.

Conclusions. EF is more sensitive at detecting systolic dysfunction over dP/dt max in a swine model of MI. Although adjustment with EDP and HR improved the predictive accuracy of dP/dt max, it remained less powerful compared with EF. The results of the present study suggest that EF is a comprehensive parameter of contractility, HR, and LV remodeling. While dP/dt max may be a useful tool to assess contractility within the same animal, EF is more suited for interanimal comparisons of systolic function after MI.

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

REFERENCES


