Assessment of left ventricular diastolic function by early diastolic mitral annulus peak acceleration rate: experimental studies and clinical application

Qinyun Ruan,1 Liyun Rao,3 Katherine J. Middleton,2 Dirar S. Khoury,3 and Sherif F. Nagueh2

1First Affiliated Hospital of Fujian Medical University, Fuzhou, China; and 2Methodist DeBakey Heart Center and 3Section of Cardiology, Department of Medicine, Baylor College of Medicine, Houston, Texas

Submitted 6 June 2005; accepted in final form 28 September 2005

Ruan, Qinyun, Liyun Rao, Katherine J. Middleton, Dirar S. Khoury, and Sherif F. Nagueh. Assessment of left ventricular diastolic function by early diastolic mitral annulus peak acceleration rate: experimental studies and clinical application. J Appl Physiol 100: 679–684, 2006.—We sought to examine the hemodynamic determinants and clinical application of the peak acceleration rate of early (Ea) diastolic velocity of the mitral annulus by tissue Doppler. Simultaneous left atrial and left ventricular (LV) catheterization and Doppler echocardiography were performed in 10 dogs. Preload was altered using volume infusion and caval occlusion, whereas myocardial lusitropic state was altered with dobutamine and esmolol. The clinical application was examined in 190 consecutive patients (55 control, 41 impaired relaxation, 46 pseudonormal, and 48 restrictive LV filling). In addition, in 60 consecutive patients, we examined the relation between it and mean wedge pressure with simultaneous Doppler echocardiography and right heart catheterization. In canine studies, a significant positive relation was present between peak acceleration rate of Ea and transmitral pressure gradient only in the stages with normal or enhanced LV relaxation, but with no relation in the stages where the time constant of LV relaxation (τ) was ≥50 ms. Its hemodynamic determinants were τ, LV minimal pressure, and transmitial pressure gradient. In clinical studies, peak acceleration rate of Ea was significantly lower in patients with impaired LV relaxation irrespective of filling pressures (P < 0.001) and with similar accuracy to peak Ea velocity (area under the curve for septal and lateral peak acceleration rates: both 0.78) in identifying these patients. No significant relation was observed between peak acceleration rate and mean wedge pressure. Peak acceleration rate of Ea appears to be a useful index of LV relaxation but not of filling pressures and can be applied to identify patients with impaired LV relaxation irrespective of their filling pressures.

Animal preparation. After the Baylor College of Medicine Animal Research Committee approved the study, 10 healthy adult mongrel dogs (weight 19–28 kg) were anesthetized with pentobarbital sodium (30 mg/kg), intubated, and mechanically ventilated with an external respirator. After a midline sternotomy, the heart was exposed, and after calibration, a high-fidelity 5-Fr pressure catheter (Millar Instruments, Houston, TX) was introduced into the left atrium (LA) through its appendage. Likewise, to measure LV pressures, a calibrated 5-Fr 12-electrode pressure catheter (Millar) was advanced into the LV by crossing the aortic valve (positioned along the LV long axis). Surface electrocardiogram (lead II), atrial, and ventricular pressure signals were simultaneously acquired on a computer-based data-acquisition system, and LA and LV pressures were digitized with recordings acquired at end expiration. The inferior vena cava (IVC) was dissected and a ring was placed around it to allow for gradual occlusion of the vein.

Hemodynamic measurements. LV minimal pressure and LVEDP, maximal instantaneous diastolic transmitial pressure gradient and LA mean pressure were noted. Also ascertained were the first derivatives of LV pressure in diastole (−dP/dt) and the time constant (τ) of LV relaxation (13). Echocardiography. The animals were imaged from the epicardium by use of an ultrasound system equipped with TDI capability. In the apical four-chamber view, pulse-wave (PW) Doppler was applied to record mitral inflow at the valve tips (intraobserver variability for measuring mitral peak E velocity: 3 ± 1%). The TD program was applied in PW Doppler to record mitral anular velocities at the septal and lateral areas (6). The peak velocity of Ea (intraobserver variability 5 ± 2%) at the above sites of the annulus was measured under the different loading conditions. The time interval between the peak of R wave and onset of mitral E velocity and between peak of R wave and onset of Ea at the four areas of the mitral annulus were measured. Subsequently the difference between these time intervals (TEa − Et) was calculated (10) for each of the four areas and an average value was derived (intraobserver variability 4 ± 2%, interobserver variability 6 ± 2%).

The peak acceleration rate of Ea velocity was derived by the computer after the Ea velocity was traced. The computer algorithm used divided the time from the onset of Ea to its peak into 20 equal intervals and measured the change in velocity per unit of time in each interval and reported the highest value (interobserver variability 8 ±

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
Ea and its peak and mean acceleration rates were correlated with hemodynamic parameters by regression analysis. Stepwise regression was then used to determine the hemodynamic parameters that correlated best with the individual Doppler variables. The study was powered to detect a correlation coefficient of at least 0.4 between the transmitral pressure gradient and peak acceleration rate of Ea (power = 80%, $P = 0.05$). Repeated-measures ANOVA with Bonferroni correction was used to compare Doppler and hemodynamic parameters at the different lusitropic states (baseline, dobutamine, and esmolol) and loading conditions.

ANOVA with Bonferroni correction was used to compare the control group with each of the other three groups (IR, PN, and Res). Receiver operator characteristic curves were applied to examine the accuracy of TDI signals in identifying patients with increased LV filling pressures. Linear regression analysis was used to relate mean wedge pressure to Doppler measurements. Significance was set at a $P$ value $<0.05$.

**RESULTS**

**Animal Studies**

**Hemodynamics and Doppler measurements.** Table 1 summarizes the hemodynamic and TD data (average of the two annular sites shown in the table because similar observations were noted at each separate site) at the different experimental stages. Volume expansion resulted in an increase in LV filling pressures, annular Ea, and its peak and mean acceleration rate. IVC occlusion resulted in significantly opposite changes in the above measurements.

Dobutamine infusion resulted in shorter $\tau$ along with an increase in annular Ea and its peak and mean acceleration rate. Esmolol infusion resulted in significantly opposite changes in the above measurements. In all of the above interventions, only esmolol infusion resulted in a significant change in $T_{\text{Ea,E}}$ prolonging it.

**Relation of TD signals to LV hemodynamics.** In individual dogs, the correlation coefficient of Ea velocity and peak and mean acceleration rate of Ea with LA mean pressure ranged from 0.4 to 0.75 ($P$ value range 0.1–0.03). As for LV relaxation, peak Ea velocity ($r = -0.76$), and its mean ($r = -0.73$) and peak acceleration rates ($r = -0.75$) exhibited strong relations to $\tau$ (all $P < 0.001$) and $-dP/dt$ (r ranging from 0.65 to 0.79, all $P < 0.001$) (Fig. 1). Peak and mean acceleration rates of Ea were also significantly related to LV minimal pressure ($r = -0.68$ and $r = -0.65$, respectively, both $P < 0.01$).

The relation of peak acceleration rate of Ea to the transmitral pressure gradient was evaluated in all the experimental stages where $\tau$ was $\geq 50$ ms and in those where $\tau$ was $< 50$ ms. There was no significant relation between peak acceleration rate of Ea

4%). In an attempt to simplify the measurement of acceleration rate of Ea, we also calculated the mean acceleration rate as the Ea velocity divided by acceleration time. Interobserver variability was $6 \pm 3\%$.

**Experimental protocols.** Initially LA pressure was increased with intravenous infusion of isotonic saline and decreased with IVC external compression. Both the infusions and compressions were performed in a sequential manner with data acquired at predetermined increments and decrements of mean LA pressure. After achieving a stable hemodynamic state at each LA pressure level, the LA and the LV pressures and Doppler data were acquired. After a stable hemodynamic state was achieved, to evaluate the influence of LV relaxation on Ea and its peak acceleration rate, dobutamine was administered at a dose of $5 \mu g \cdot kg^{-1} \cdot min^{-1}$ with Doppler and pressure data were acquired. Dobutamine infusion was then terminated, and, after the animals returned to their baseline state, esmolol with its negative lusitropic properties was administered (0.5 mg/kg iv) with subsequent reacquisition of data. To assess the possible interaction between atrial pressure and ventricular relaxation on the peak acceleration rate of Ea, fluid administration and IVC compression were repeated during dobutamine and esmolol infusion.
Table 1. Hemodynamics and TD velocities during volume loading, IVC occlusion, and dobutamine and esmolol infusions

<table>
<thead>
<tr>
<th>Hemodynamic Parameter</th>
<th>Baseline</th>
<th>Volume Loading</th>
<th>IVC Occlusion</th>
<th>Dobutamine</th>
<th>Esmolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV stroke volume, ml</td>
<td>20±5(^a)</td>
<td>28±4(^b)</td>
<td>14±4</td>
<td>23±4.5(^d)</td>
<td>16±5.4</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>115±6</td>
<td>115±8</td>
<td>118±12</td>
<td>136±3(^f)</td>
<td>103±8(^g)</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>5±3(^a)</td>
<td>11±5(^b)</td>
<td>2.1±0.6(^b)</td>
<td>2.6±0.8(^b)</td>
<td>14.5±3(^b)</td>
</tr>
<tr>
<td>LA mean pressure, mmHg</td>
<td>7±4(^a)</td>
<td>11±6.4(^b)</td>
<td>3±2(^b)</td>
<td>3.5±2.2(^b)</td>
<td>15±4(^b)</td>
</tr>
<tr>
<td>(\tau), ms</td>
<td>42±10</td>
<td>44±9</td>
<td>39±8</td>
<td>26±7(^e)</td>
<td>87±8(^e)</td>
</tr>
<tr>
<td>LV (-\frac{dP}{dt}), mmHg/s</td>
<td>1,840±365(^a)</td>
<td>1,925±400(^b)</td>
<td>1,420±400(^d)</td>
<td>3,720±420(^d)</td>
<td>725±367</td>
</tr>
<tr>
<td>Ea, cm/s</td>
<td>5.2±1(^a)</td>
<td>5.9±1.2(^b)</td>
<td>4.5±1(^e)</td>
<td>8.8±0.8(^e)</td>
<td>3±0.7(^e)</td>
</tr>
<tr>
<td>Ea mean acceleration rate, cm/s(^2)</td>
<td>74±15(^a)</td>
<td>90±19(^b)</td>
<td>63±20(^d)</td>
<td>100±21(^d)</td>
<td>53±20(^d)</td>
</tr>
<tr>
<td>Ea peak acceleration rate, cm/s(^2)</td>
<td>105±25(^a)</td>
<td>129±21(^b)</td>
<td>91±19(^d)</td>
<td>143±33(^d)</td>
<td>69±18(^d)</td>
</tr>
<tr>
<td>(T_{\text{Ea-E}}), ms</td>
<td>1.5±5</td>
<td>0.5±5</td>
<td>1.2±5</td>
<td>0±3</td>
<td>23±4(^d)</td>
</tr>
</tbody>
</table>

Values are means ± SD. TD, tissue Doppler; IVC, inferior vena cava; LV, left ventricular; LVEDP, LV end-diastolic pressure; LA, left atrial; \(\tau\), time constant of LV relaxation; LV \(\frac{dP}{dt}\), first derivative of LV pressure in diastole; Ea, early diastolic annular velocity; \(T_{\text{Ea-E}}\), Ea-E time interval. \(^a\)P < 0.05 vs. volume loading, IVC occlusion, dobutamine, and esmolol stages; \(^b\)P < 0.05 vs. IVC occlusion, dobutamine and esmolol stages; \(^c\)P < 0.05 vs. baseline, volume loading, and IVC occlusion stages; \(^d\)P < 0.05 vs. esmolol stage; \(^e\)P < 0.05 vs. baseline, volume infusion, IVC occlusion, and esmolol; \(^f\)P < 0.05 vs. baseline, volume loading, IVC occlusion, and dobutamine stages.

The mean age of this group was 60±15 yr. The mean arterial pressure was 81±15 mmHg, whereas the mean PA pressure was 33±10 mmHg. Mitral inflow pattern was that of IR in 20 patients, PN filling in 25 patients, and restrictive filling in 15 patients. Mean PCWP was 20±10 (range 5–45) mmHg. A nonsignificant trend for an inverse relation was noted between peak acceleration rate and septal and mitral Ea velocity (peak acceleration rate: \(r = -0.23\), P = 0.08, Fig. 5). However, significant correlations were noted with mitral E/A ratio (\(r = 0.5\), P < 0.05), E/Ea ratio (t-test P < 0.05 for control group vs. each of the other three groups). Figure 3 illustrates examples of TDI signals in four representative cases. Table 3 summarizes the accuracy of peak Ea velocity and its acceleration rate in identifying patients with impaired LV relaxation despite elevated filling pressures (ROC curves shown in Fig. 4).

**Fig. 1.** Relation of time constant of LV relaxation (\(\tau\)) vs. septal peak early diastolic annular (Ea) velocity (left) and its peak acceleration rate (right).

**Fig. 2.** Relation of peak acceleration rate of Ea vs. transmitral pressure gradient. Solid line and \(\bullet\), stages where \(\tau\) was <50 ms; dashed line and \(\circ\), stages where \(\tau\) was ≥50 ms. In the presence of normal or enhanced relaxation, a direct significant relation was present (\(r = 0.71\), P < 0.01), whereas with impaired relaxation, no relation was observed between peak acceleration rate of Ea and transmitral pressure gradient (P > 0.3).
LV EF, % 65 ± 3\textsuperscript{a} 73 ± 28\textsuperscript{e,c} 81 ± 26 89 ± 22
PA systolic pressure, mmHg 30 ± 3\textsuperscript{a} 35 ± 13\textsuperscript{c} 44 ± 10.5 48 ± 10
Mitral E/A ratio 1.1 ± 0.1 0.7 ± 0.16\textsuperscript{e} 1.4 ± 0.29 3 ± 0.9\textsuperscript{b}
Deceleration time, ms 220 ± 86\textsuperscript{a} 252 ± 84\textsuperscript{d} 188 ± 69 169 ± 43
Pulmonary veins, SFF 0.6 ± 0.1\textsuperscript{d} 0.59 ± 0.1\textsuperscript{d} 0.52 ± 0.1\textsuperscript{e} 0.42 ± 0.1
Ar-A duration, ms 0 ± 8\textsuperscript{a} 18 ± 10\textsuperscript{d} 45 ± 11\textsuperscript{e} 58 ± 10
Septal Ea, cm/s 9.3 ± 3.2\textsuperscript{a} 5.2 ± 2.1 5.5 ± 2.3 4.7 ± 1.5
Septal peak acceleration rate, cm/s\textsuperscript{2} 259 ± 99\textsuperscript{a} 159 ± 88 178 ± 87 149 ± 75
Lateral Ea, cm/s 11.3 ± 4.7\textsuperscript{a} 7.5 ± 2.5 6.9 ± 2.7 7.4 ± 3.2
Lateral mean acceleration rate, cm/s\textsuperscript{2} 161 ± 68\textsuperscript{a} 98 ± 38 134 ± 49 100 ± 48
Lateral peak acceleration rate, cm/s\textsuperscript{2} 311 ± 116\textsuperscript{a} 185 ± 79 210 ± 105 193 ± 112
T\textsubscript{Ea-E,m s 3} 3 ± 5\textsuperscript{a} 29 ± 5 33 ± 3 40 ± 3

Values are means \pm SD. \textsuperscript{a}P < 0.05 vs. impaired relaxation (IR), pseudonormal (PN), and restrictive filling (Res) groups; \textsuperscript{b}P < 0.05 vs. control, IR, and PN groups; \textsuperscript{c}P < 0.05 vs. control and PN groups; \textsuperscript{d}P < 0.05 vs. PN and Res groups; \textsuperscript{e}P < 0.05 vs. Res group. Ar-A, difference in atrial velocity duration between pulmonary vein and mitral inflow.

Fig. 3. Examples of mitral inflow and tissue Doppler imaging (TDI) at septal annulus from patients in each of the 4 groups. Note the reduced Ea velocity in patients with pseudonormal (PN) and restrictive (Res.) left ventricular (LV) filling, despite increased LV filling pressures. Peak acceleration rate of Ea in the normal subject (NL) was 330 cm/s\textsuperscript{2}, whereas it was reduced to 140 cm/s\textsuperscript{2} in the patient with impaired relaxation (IR) pattern, to 138 cm/s\textsuperscript{2} in the patient with PN pattern, and to 160 cm/s\textsuperscript{2} in the patient with Res filling.

DISCUSSION

The animal experiments show that the hemodynamic determinants of peak acceleration rate of Ea are transmitral pressure gradient, LV minimal pressure, and LV relaxation. The relation between peak acceleration rate of Ea and transmitral pressure gradient is a direct linear relation only in the presence of normal or enhanced LV relaxation, but no direct correlation was noted in the presence of impaired LV relaxation. The clinical studies confirm and extend these animal observations. The peak acceleration rate of Ea, at either side of the mitral annulus, in patients with impaired LV relaxation (IR, PN, and Res groups) was significantly lower than in the age-matched control group. Overall its accuracy in identifying patients with impaired relaxation and elevated filling pressures was similar to peak Ea velocity. Furthermore, in the subgroup with simul-
taneous invasive measurements, no relation was noted between mean PCWP and peak acceleration rate of Ea.

Animal Studies

We used the PW signal at each side of the mitral annulus to calculate the peak acceleration rate of Ea. PW, unlike color Doppler, has the major advantage of superior temporal resolution, which suits well the need to calculate the peak acceleration rate given the very short time (frequently <50 ms) when acceleration of Ea is occurring. An additional advantage to our method lies in the higher sampling rate afforded by using 20 intervals for deriving the peak acceleration rate, making it much less likely to miss the highest acceleration rate when limiting the analysis to longer time intervals.

In the previous study (4), the peak acceleration rate of the Ea velocity, particularly at the septal side of the mitral annulus, increased significantly with blood infusion but was not altered by dobutamine or metoprolol administration. Unlike these findings, we noted that changes in the myocardial lusitropic state with either dobutamine or esmolol were effective in producing significant changes in peak acceleration rate of Ea. The magnitude of change in Ea peak acceleration rate was comparable to the change in peak Ea velocity induced by these drugs. Furthermore, the peak acceleration rate of Ea had a significant inverse correlation with the invasive measurements of LV relaxation that was almost identical to those of Ea peak velocity.

Table 3. Accuracy of peak Ea velocity and acceleration rate of Ea in identifying patients with impaired LV relaxation despite elevated filling pressures

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Area under ROC curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septal Ea (&lt;5.6 cm/s)</td>
<td>66</td>
<td>88</td>
<td>0.875 (0.81–0.94)*</td>
</tr>
<tr>
<td>Septal peak acceleration rate (&lt;195.5 cm/s²)</td>
<td>76</td>
<td>75</td>
<td>0.78 (0.7–0.86)*</td>
</tr>
<tr>
<td>Lateral Ea (&lt;8.6 cm/s)</td>
<td>79</td>
<td>75</td>
<td>0.82 (0.75–0.9)*</td>
</tr>
<tr>
<td>Lateral peak acceleration rate (&lt;252 cm/s²)</td>
<td>74</td>
<td>72</td>
<td>0.78 (0.71–0.86)*</td>
</tr>
</tbody>
</table>

*P < 0.001; numbers between parenthesis refer to 5–95% confidence intervals. ROC, receiver operator characteristics.

The relation between the peak acceleration rate of Ea and filling pressures is a complicated one and overall very similar to that of the peak Ea velocity itself, as previously reported in animal (3, 7) and human studies (1, 2). The relation between LA pressure and peak acceleration rate of Ea in the presence of cardiac dysfunction is very important for the clinical application of Ea acceleration rate in the clinical setting, because the assessment of LV filling pressures is frequently needed in patients with cardiac disease. The previous animal work was limited in that regard owing to the occurrence of only small changes in LA pressure with beta-blockers. However, the peak acceleration rate of Ea can be used to predict LV filling pressures in normal subjects, given the direct relation between this Doppler measurement and preload in normal states.

On the other hand, our animal study provides the pathophysiological reasons for not applying the peak acceleration rate of Ea to the estimation of LV filling pressures, in the presence of impaired LV relaxation (Fig. 2). Similar to the acceleration rate of Ea, T_{Ea-E} duration was altered by esmolol, but, unlike the acceleration rate, IVC occlusion and volume infusion had no significant effect on this time interval. Overall these results are similar with the observations of Hasegawa et al. (3), who noted that Ea was progressively delayed after LA to LV pressure crossover and was significantly related to \( \tau \) in an animal model of pacing-induced heart failure.

Human Studies

In the human studies, the mean and peak acceleration rate of Ea at either side of the mitral annulus were significantly lower in patients with impaired LV relaxation, irrespective of LV filling pressures. It is interesting that the relation between mean wedge pressure and peak acceleration rate of Ea, shown in Fig. 5, in patients with cardiac disease was very similar to that observed in the canine experiments between transmitral pressure gradient and peak acceleration rate of Ea when LV relaxation was impaired as shown in Fig. 2 (dashed line and open circles).

Our study also shows that the accuracy of peak acceleration rate of Ea at either side of the mitral annulus for identifying patients with impaired LV relaxation despite elevated filling pressures (PN and Res groups) is similar to that of the peak Ea velocity.
velocity. There was no incremental information gained over peak Ea velocity by measuring its acceleration rate. Given the above findings and the complexity of measurement of acceleration rate, peak Ea velocity rather than its acceleration rate is more suitable for the daily application in the laboratory.

REFERENCES


