Non-invasive assessment of left ventricular relaxation during atrial fibrillation using mitral flow propagation velocity†

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Aims To elucidate the usefulness of the early diastolic mitral flow propagation velocity (Vp) obtained from colour M-mode Doppler for non-invasively assessing left-ventricular (LV) relaxation during atrial fibrillation (AF).

Methods and results Ten healthy adult dogs were studied to correlate Vp with the invasive minimum value of the first derivative of LV pressure decay (dP/dtmin) and the time constant of isovolumic LV pressure decay (τ) at baseline, during rapid and slow AF, and during AF after inducing myocardial infarction. There were significant positive and negative curvilinear relationships between Vp and dP/dtmin and τ, respectively, during rapid AF. After slowing the ventricular rate, the average value of Vp increased, while dP/dtmin increased and τ decreased. After inducing myocardial infarction, the average value of Vp decreased, while dP/dtmin decreased and τ increased.

Conclusion The non-invasively obtained Vp evaluates LV relaxation even during AF regardless of ventricular rhythm or the presence of pathological changes.

KEYWORDS
Mitral flow propagation velocity;
Atrial fibrillation;
The first derivative of left ventricular pressure decay;
The time constant of isovolumic left ventricular pressure decay

Introduction
Atrial fibrillation (AF) increases the risk of congestive heart failure,1 therefore, the identification and the assessment of diastolic dysfunction during AF are critical. Many patients with heart failure have been found to have left ventricular (LV) diastolic rather than systolic dysfunction, and it is increasingly recognized that LV diastolic dysfunction plays an important role in the pathophysiology of heart failure.2 Non-invasive evaluation of the LV diastolic function during normal sinus rhythm has been performed using conventional Doppler techniques.3 However, their use has been limited in subjects with AF because of the lack of atrial contraction waves and beat-by-beat alterations of the preload.4 The early diastolic mitral flow propagation velocity (Vp) obtained from colour M-mode Doppler has been reported to be a useful parameter which can supplement Doppler mitral inflow and pulmonary venous flow velocities for assessing LV relaxation in subjects with sinus rhythm.5–10 The Vp has a strong negative curvilinear relationship with the time constant of isovolumic LV pressure decay (τ)6,7,9 and is relatively independent of preload in subjects with sinus rhythm.5,8 The loading condition should be relatively constant in one individual with normal sinus rhythm, therefore the Vp and τ could be relatively constant. However, there has been no adequate validation of this index in subjects with AF and beat-by-beat variation of the preload.5 The beat-by-beat changes in RR intervals in AF may cause beat-by-beat changes in the preload. Those changes in the preload should cause beat-by-beat changes in the Vp and τ.

The selective atrioventricular nodal post-ganglionic vagal nerve stimulation (PGVS) is one of the procedures which can slow ventricular rate during AF. We have reported that PGVS during AF improved both LV contractility and relaxation in the animal experiment as evidenced by increase

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and decrease in the average values of \( dP/dt_{\text{min}} \) and \( \tau \), respectively.11–13

The purpose of the present study was to validate \( V_p \) as a non-invasive parameter of LV relaxation in subjects with AF, by correlating \( V_p \) with invasive haemodynamic indices of LV relaxation, such as \( dP/dt_{\text{min}} \) and \( \tau \), during changes induced by PGVS and myocardial infarction.

**Methods**

The study protocol was approved by the Animal Research Committee of the Cleveland Clinic Foundation and is in compliance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

**Surgical preparation**

The study was performed on 10 healthy adult mongrel dogs weighing 25–35 kg, instrumented as previously described.11–14 Briefly, animals were placed in the supine position, premedicated with thiopental sodium (20 mg/kg IV), intubated, and ventilated with room air supplemented with oxygen as needed by a respirator. Anaesthesia was maintained with an inhalation mixture of oxygen and isoflurane (1.0–2.0%). Surface ECG, volume status, arterial blood gases, and body temperature were monitored throughout the experiments.

A micromanometer-tipped catheter (Millar Instruments; Houston, TX) was used to acquire the LV pressure curve. A median sternotomy was performed and custom-made pacing electrodes were sutured to the right high atrium and right ventricular apex for recording and bipolar pacing. Similar bipolar electrodes were sutured to two epicardial fat-pads that contain parasympathetic neural pathways selectively innervating the sinus node and the atrioventricular node, respectively.

**Electrical stimulation and data acquisition**

After the surgical procedures were completed, a stabilization period of 30 min at normal sinus rhythm was allowed. Then, baseline recordings at normal sinus rhythm were acquired. AF was induced by a manoeuvre as previously reported.11 First, AF was triggered by brief burst (5–10 s) of right atrial pacing (5–10 mA, 1 ms pulses at 20 Hz). Second, AF was maintained by sinus node fat-pad stimulation (4–7 mA, 50 \( \mu \)s pulse duration at 20 Hz), which provided selective vagal stimulation to the sinus node and surrounding atrium. While AF was maintained, the atrioventricular fat-pad was subsequently stimulated to achieve slow ventricular rate, a pro-atrium. While AF was maintained, the atrioventricular fat-pad was subsequently stimulated to achieve slow ventricular rate, a pro-atrium.

Atrial pacing and nerve stimulation were performed using a programmable stimulator (Master-8, AMPI).

All signals were amplified, filtered, digitized, and continuously displayed on a monitoring system and the electrical and haemodynamic data were recorded into data acquisition boards as previously described.14 The electrical, haemodynamic, and echocardiographic data were simultaneously acquired at baseline sinus rhythm, during triggered AF and during AF with subsequent PGVS.

**Induction of myocardial infarction**

After the primary data acquisition was completed, the electrical stimulation was temporarily removed to restore sinus rhythm. Then, the distal portion of the left anterior descending coronary artery was ligated to induce myocardial infarction and LV systolic dysfunction. The effect of ligation was visually confirmed by the akinetic wall motion abnormality in the area of the ligated coronary artery using two-dimensional echocardiography.15 After a stabilization period of 60 min, AF was triggered again and the ventricular rate was slowed using the same PGVS manoeuvre as described earlier. Similar data acquisition at sinus rhythm, during triggered AF and during AF with PGVS was performed.

**Haemodynamic assessments**

The maximum value of the first derivative of LV pressure curve (\( dP/dt_{\text{max}} \)), \( dP/dt_{\text{min}} \), and \( \tau \) were obtained by digitizing the LV pressure curve off-line.14 The \( \tau \) was determined by fitting the pressure-time data (from the point of \( dP/dt_{\text{min}} \) to LV pressure 5 mmHg higher than next LV end-diastolic pressures) to the equation: 

\[
P(t) = (P_0 - P_b)e^{-t/\tau} + P_b,
\]

where \( P_0 \) is the pressure decay asymptote, \( P_b \) is the pressure at \( dP/dt_{\text{min}} \), \( t \) is time referenced to time of \( dP/dt_{\text{min}} \) occurrence.16 An interval of \( > 25 \text{ ms} \) was considered necessary to calculate \( \tau \). The RR intervals were measured from the right-ventricular electrocardiogram.

**Echocardiographic assessments**

Epicardial echocardiography was performed using commercially available equipment (Sequoia C512, Siemens Medical Solutions; Mountain View, CA) with a 3.5 MHz phased array transducer. LV ejection fraction (EF) was calculated using the modified Simpson method according to the American Society of Echocardiography recommendation.15 The Doppler stroke volume (SV) was calculated as a product of the velocity-time integral of the LV outflow Doppler profile recorded from the standard LV five-chamber view and LV outflow cross-sectional area calculated from LV outflow tract diameter measured from parasternal long-axis view during mid-systole, assuming a circular geometry.

From the four-chamber view, the colour Doppler flow mapping of the mitral inflow was displayed and colour M-mode recordings were acquired after aligning the cursor in the direction of the inflow jet (generally slightly lateral to the standard four-chamber view). The \( V_p \) was measured from the recording of colour M-mode as the slope of the first aliasing velocity (45 cm/s) from the mitral tips to 4 cm distally into the LV cavity in early diastole17 and was correlated with \( dP/dt_{\text{min}} \) and \( \tau \).18 In order to obtain a reliable measurement of \( V_p \), careful attention was made to avoid measuring intracavitary flow originating before the onset of mitral inflow.19

To carefully identify corresponding beats in the colour M-mode images and LV pressure recordings, a timing marker signal was recorded both within the colour M-mode images and the data acquisition boards simultaneously as previously described.20

Every study was finished within 4 h \( \pm 18 \text{ min} \) from the beginning of the study. All the parameters in each animal were measured as an average of at least 20 consecutive cardiac cycles. In all the colour M-mode images \( V_p \) was feasible to measure. Echocardiographic analysis was performed by a cardiologist who had no knowledge of haemodynamic data.

**Statistical analysis**

Data are expressed as mean \( \pm SD \). To test the hypothesis of whether \( V_p \) could be used as a non-invasive index of LV relaxation, polynomial regression analysis were performed between \( V_p \) and \( dP/dt_{\text{min}} \) and \( \tau \). Also, regression analysis was performed between \( V_p \) and \( dP/dt_{\text{min}} \) and \( \tau \), allowing for the differences between animals.21

The differences in the LV systolic and diastolic parameters at sinus rhythm before and after coronary ligation were analysed using a Student’s paired t-test. Serial changes in the RR intervals and LV systolic and diastolic parameters during sinus rhythm, triggered AF and subsequent PGVS before and after coronary ligation were analysed by one-way repeated measured analysis of variance (ANOVA). A \( P \)-value \(< 0.05 \) was considered statistically significant.

The authors had full access to the data and took responsibility for its integrity. All authors have read and agree to the manuscript as written.
Results

Validation of mitral flow propagation velocity as a parameter of left-ventricular relaxation during atrial fibrillation

After initial trigger of AF by burst atrial stimulation, as shown in the Figure 1, there was a significant positive curvilinear relationship between dP/dt_{min} and V_p (r = 0.71 ± 0.10, P < 0.05) in all the animals. A regression analysis between dP/dt_{min} and V_p, allowing for the between-animals differences was performed with the regression equation:

\[ V_p = 420 + \Sigma b_i D_i + 34.9 \cdot (dP/dt_{min}) \]

where Di is (i) 1 if animal i (i<10), (ii) -1 if animal 10, and (iii) 0 otherwise, and bi is coefficient for each Di.

There was a significant negative curvilinear relationship between t and V_p (r = 0.69 ± 0.14, P < 0.01) (Figure 2). A regression analysis between t and V_p, allowing for the between-animals differences was performed with the regression equation:

\[ V_p = 97.9 + \Sigma b_i D_i - 0.90 \cdot t \]

where Di is (i) 1 if animal i (i<10), (ii) -1 if animal 10, and (iii) 0 otherwise, and bi is coefficient for each Di. There were significant relationships between dP/dt_{min}, t and V_p even after accounting for the between-animals differences.

Figure 3 shows a representative recording from one animal. Note that the second beat comes so early that it does not produce enough pressure to cause ejection, but does allow subsequent filling, with very prolonged t and diminished V_p. The t was smaller and the dP/dt_{min} was

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Figure 1  Relationship between the minimum value of the first derivative of left ventricular pressure curve (dP/dt_{min}) and the early diastolic mitral flow propagation velocity (V_p) in each animal. There was a positive curvilinear relationship between dP/dt_{min} and V_p in each animal.
greater when the Vp was greater in the corresponding cardiac cycles. Thus, changes in Vp detected beat-by-beat variability in LV relaxation due to changes in cycle-length during AF.

Effects of atrial fibrillation and subsequent post-ganglionic vagal nerve stimulation in left-ventricular systolic and diastolic function parameters

The RR intervals significantly decreased by triggered AF and increased by subsequent PGVS (Table 1). Corresponding to the increase in the ventricular rate by triggering AF, all the LV systolic parameters including EF, SV, and dP/dt\textsubscript{max}, first decreased significantly, thereafter increased significantly after slowing ventricular rate by subsequent PGVS. The dP/dt\textsubscript{min} decreased and \tau increased significantly with rapid AF, and subsequently increased and decreased significantly by PGVS, respectively. Similarly, the Vp decreased significantly with rapid AF and increased significantly by PGVS.

Effects of myocardial infarction during atrial fibrillation and subsequent post-ganglionic vagal nerve stimulation

After ligation of the left anterior descending coronary artery during sinus rhythm, there was deterioration in all LV systolic function parameters compared with baseline sinus rhythm (Table 1). These systolic parameters further deteriorated significantly with shorter RR intervals during rapid AF and improved significantly with longer RR intervals by subsequent PGVS (Table 1). Similarly, the dP/dt\textsubscript{min} decreased and \tau increased during sinus rhythm after coronary ligation compared with baseline, with further deterioration during rapid AF and improvement by subsequent PGVS. The Vp at

Figure 2  Relationship between the time constant of isovolumic left ventricular pressure decay (\tau) and the early diastolic mitral flow propagation velocity (Vp). There was a negative curvilinear relationship between the \tau and Vp in each animal.
sinus rhythm during myocardial infarction significantly decreased compared with \( V_p \) at baseline. It further decreased during rapid AF and significantly increased by subsequent PGVS despite continued myocardial infarction.

**Discussion**

The present study reports three major findings. First, from the simultaneous beat-by-beat recording of colour M-mode echocardiography and left ventricular (LV) pressure during AF, the present study has shown the early diastolic mitral flow propagation velocity (\( V_p \)) has significant positive and negative curvilinear relationships with \( \frac{dP}{dt_{\text{min}}} \) and \( \tau \), respectively. Second, the average value of \( V_p \) accurately evaluated deterioration of the LV relaxation induced by rapid AF as well as its improvement by slowing ventricular rate both in the normal and the ischaemic heart. Third, this was the first study to precisely assess beat-by-beat based LV filling in subjects with AF using \( V_p \).

The \( V_p \) and the early diastolic tissue Doppler myocardial velocity have been proposed as better parameters for assessing LV relaxation than conventional Doppler mitral inflow and pulmonary venous flow velocities, because \( V_p \) and the early diastolic tissue Doppler myocardial velocity are considered to be less dependent on preload during sinus rhythm. The \( V_p \) has been reported to have negative curvilinear relationship with the \( \tau \) in subjects with normal sinus rhythm. The ratio of early diastolic mitral inflow velocity over either early diastolic tissue Doppler myocardial velocity or \( V_p \) have been reported to be useful for predicting LV filling pressure during AF. However, there have been very few reports applying these indices on subjects of AF with beat-by-beat variation in cardiac cycle length. The \( V_p \) is a very simple technique which could be measured easily.

In animal experiments during sinus rhythm, we demonstrated that LV relaxation was the main physiological determinant of \( V_p \). We have also reported that the duration of the preceding LV filling time during AF determined LV end-diastolic volume and the following peak systolic LV pressure and thereby \( \frac{dP}{dt_{\text{min}}} \) and \( \tau \). Thus, LV relaxation during AF varies on a beat-by-beat basis according to the changes in the loading condition of the preceding beat. The previous assessments of LV relaxation during AF have only assessed average values of the parameters for several consecutive cardiac beats. The present study was the first to show the relationship between \( V_p \) and \( \tau \) and \( \frac{dP}{dt_{\text{min}}} \) in AF during data obtained from beat-by-beat analysis in single individuals. Thus, \( V_p \) can be used as a parameter, which could evaluate LV relaxation on a beat-by-beat basis during AF. The changes in the average values of \( V_p \) from 20 or more consecutive cardiac beats have shown similar trends in the changes in \( \frac{dP}{dt_{\text{min}}} \) and \( \tau \) by triggered rapid AF and by slowing ventricular rate applying PGVS. Therefore, average \( V_p \) can evaluate LV relaxation independent of ventricular rhythm and cardiac cycle length irregularity.

The ligation of the left-anterior descending coronary artery created an anterior regional wall motion abnormality and deterioration of LV performance during sinus rhythm. Rapid AF further deteriorated LV relaxation, while PGVS improved it by slowing ventricular rate. The impairment of

<table>
<thead>
<tr>
<th>RR (ms)</th>
<th>EF (%)</th>
<th>SV (mL)</th>
<th>( \frac{dP}{dt_{\text{max}}} ) (mmHg/s)</th>
<th>( \frac{dP}{dt_{\text{min}}} ) (mmHg/s)</th>
<th>( \tau ) (ms)</th>
<th>( V_p ) (cm/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base-SR</td>
<td>405 ± 15</td>
<td>51 ± 9</td>
<td>34.2 ± 9.0</td>
<td>3792 ± 389</td>
<td>3096 ± 204</td>
<td>35.0 ± 5.0</td>
</tr>
<tr>
<td>Base-AF</td>
<td>202 ± 73</td>
<td>40 ± 4</td>
<td>19.1 ± 4.7</td>
<td>3099 ± 434</td>
<td>1416 ± 1038</td>
<td>77.6 ± 18.9</td>
</tr>
<tr>
<td>Base-AF/PGVS</td>
<td>432 ± 137</td>
<td>49 ± 8</td>
<td>23.8 ± 5.5</td>
<td>3216 ± 541</td>
<td>2220 ± 687</td>
<td>55.2 ± 33.0</td>
</tr>
<tr>
<td>Ligation-SR</td>
<td>2219 ± 37*</td>
<td>38 ± 3*</td>
<td>24.9 ± 12.4*</td>
<td>2711 ± 778*</td>
<td>2643 ± 243*</td>
<td>41.5 ± 43.4*</td>
</tr>
<tr>
<td>Ligation-AF</td>
<td>199 ± 117</td>
<td>31 ± 8</td>
<td>17.0 ± 4.3</td>
<td>2215 ± 685</td>
<td>1759 ± 875</td>
<td>66.8 ± 19.0</td>
</tr>
<tr>
<td>Ligation-AF/PGVS</td>
<td>388 ± 207†</td>
<td>40 ± 10†</td>
<td>20.7 ± 3.4†</td>
<td>2436 ± 671†</td>
<td>2104 ± 776†</td>
<td>57.4 ± 25.1†</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD. AF, atrial fibrillation; \( \frac{dP}{dt_{\text{max}}} \), maximum value of the first derivative of left ventricular pressure curve; \( \frac{dP}{dt_{\text{min}}} \), minimum negative value of the first derivative of left ventricular pressure curve; EF, ejection fraction; SR, sinus rhythm; SV, stroke volume; \( \tau \), time constant of isovolumic left ventricular pressure decay; PGVS, post-ganglionic vagal nerve stimulation; Base, before coronary ligation; Ligation, after coronary ligation.

*\( P < 0.0001 \) vs. Base-SR.
†\( P < 0.0001 \) by one-way repeated-measured ANOVA.
LV relaxation caused by myocardial infarction and worsened by AF, manifest as a decrease in the magnitude of $\frac{dP}{dt_{\text{min}}}$ and an increase in $\tau$, was reflected in a decrease in $V_p$. Improvement in LV relaxation during PGVS, manifest as an increase in the magnitude of $\frac{dP}{dt_{\text{min}}}$ and decreased $\tau$, was accompanied by a parallel increase in $V_p$. These results thus confirm that the average $V_p$ can be used even in the pathologic heart with AF to assess impaired LV relaxation.

Colour M-mode Doppler echocardiography has previously demonstrated impaired diastolic relaxation in subjects with acute myocardial ischaemia or with coronary artery disease studied during sinus rhythm.\(^6\),\(^30\) The present study extends assessment of LV filling during AF in subjects with or without myocardial infarction using colour M-mode Doppler $V_p$.

**Limitations**

PGVS improved parameters of LV relaxation, but the data did not completely recover to the baseline data shown during sinus rhythm. Thus, LV diastolic function remained impaired during AF even when the ventricular rate was slowed by PGVS. Stages were not randomized, and thus LV diastolic function might have deteriorated simply as the experiment proceeded. However, our results suggest that the $V_p$ accurately evaluates changes of the LV relaxation both during sinus rhythm and during AF.

Determining the adequate number of cardiac beats for calculating an average value during AF has been always problematic because the results depend on the variability of the R-R interval. For routine clinical work, 5 or 10 beats may be sufficient, while another report concluded that 13 consecutive beats would be required in AF.\(^31\) In the present study, we measured at least 20 consecutive beats, and the trends obtained at base line and during triggered AF and subsequent AF with PGVS were similar to those of $\frac{dP}{dt_{\text{min}}}$ and $\tau$.

We did not record data on mitral velocity, preload, afterload, or ventricular volumes simultaneously. In our acute experimental model, the impact of LV geometric remodeling on $V_p$ could not be evaluated. It has been suggested that increased LV size leads to reduced $V_p$ independent of LV relaxation.\(^32\)

**Clinical implications**

In the clinical setting, techniques to assess LV diastolic function during AF are limited: mitral inflow and pulmonary vein flow are unreliable due to the lack of atrial contraction waves and beat-to-beat alteration of preload. Transmitral deceleration time may be prematurely truncated during AF with rapid ventricular rate. In contrast, colour M-mode images were easy to obtain and $V_p$ quick to measure. Thus, $V_p$ can be used for easily and reliably assessing LV relaxation during AF.

**Conclusions**

Colour M-mode Doppler $V_p$ correlated significantly with invasive indices of LV relaxation, $\frac{dP}{dt_{\text{min}}}$ and $\tau$ during AF on the beat-by-beat basis. The average value of $V_p$ obtained from 20 or more consecutive cardiac cycles accurately detects changes in LV relaxation induced by AF with both rapid and slow ventricular rate in the normal and pathologic heart with myocardial infarction.

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