Haemodynamic insights into the effects of ischaemia and cycle length on tissue Doppler-derived mitral annulus diastolic velocities

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ABSTRACT
In the present study, we performed simultaneous epicardial echocardiography and left heart catheterization on ten adult dogs to investigate the effects of ischaemia and tachycardia on the mitral annulus early (Ea) and late (Aa) diastolic velocities and the haemodynamic mechanisms involved. Left atrial pressure and left ventricular (LV) volumes and pressures were measured with 5 French Millar catheters. In each dog, inferior vena cava occlusion was used to alter preload and circumflex coronary artery occlusion was applied to induce ischaemia at two different cycle lengths: 450 and 550 ms. At both cycle lengths, ischaemia resulted in a reduction in LV relaxation, LV global and ipsilateral systolic function, transmitral pressure gradient (TMG), Ea and Aa (P < 0.05). The shorter cycle length was associated with a shorter tau (time constant of LV relaxation), reduced TMG and reduced septal and lateral Ea (P < 0.05 for all variables). Both septal and lateral Aa were significantly increased (P < 0.05). Ischaemia influences Ea through changes in LV relaxation, global and regional systolic function and TMG. An increase in heart rate reduces Ea, but increases Aa.

INTRODUCTION
Tissue Doppler (TD)-derived mitral annular velocities, i.e. early (Ea) and late (Aa) diastolic velocities, are useful indices of left ventricular (LV) diastolic function [1–6]. Studies have also shown that LV relaxation and early diastolic recoil strongly influence Ea, whereas preload has minimal impact in the presence of impaired relaxation [7]. Aa is primarily determined by left atrial contractility and left atrial afterload [7] and may be applied clinically to the assessment of left atrial systolic function and LV late diastolic pressures.

Several investigators have used different sites of the annulus (septal, lateral, posterior or average) to report LV diastolic function [2–6]. However, to date, there have been no studies examining the haemodynamic effects of ischaemia on annular Ea and Aa. The choice of the site of measurement is an important clinical question, since there are differences between septal and lateral corner velocities [5,6] and, in a number of cases, different conclusions may be reached depending on the site. We hypothesized that, in the presence of ischaemia and regional dysfunction, the diastolic velocities from each area depend on the underlying regional performance.

Key words: diastolic function, ischaemia, systolic function, tachycardia, tissue Doppler imaging.

Abbreviations: Ea, late diastolic velocity by tissue Doppler; AT, acceleration time of early diastolic velocity; CO, cardiac output; DT, deceleration time of early diastolic velocity; E, transmitral early diastolic velocity; Ea, early diastolic velocity by tissue Doppler; Ees, end-systolic elastance; EDP, end-diastolic pressure; EDV, end-diastolic volume; ESP, end-systolic pressure; ESV, end-systolic volume; IVC, inferior vena cava; LAD, left anterior descending coronary artery; LV, left ventricular; PRSW, preload recruitable stroke work; Sa, annular descent during systole; Sa − Ea, time between end of Sa and onset of Ea; SV, stroke volume; TD, tissue Doppler; TMG, early diastolic transmitral pressure gradient.

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as well as the global LV function. We therefore examined these velocities and their haemodynamic correlates in a controlled setting that created regional dysfunction.

In addition, understanding the haemodynamic effects of tachycardia on the annular velocities may provide valuable insights into the proper application of TD in the study of LV diastolic function when tachycardia is present. To address this question, we also investigated the haemodynamic factors influencing $E_a$ and $A_a$ in the presence of tachycardia.

**METHODS**

**Animal preparation**

After the Baylor College of Medicine Animal Research Committee approved the study, ten healthy adult mongrel dogs were anaesthetised with sodium pentobarbital (30 mg/kg of body weight), intubated and mechanically ventilated with an external respirator. After a midline sternotomy, the heart was exposed in a pericardial cradle and a pair of pacing electrodes sutured to the right atrial appendage. Electrodes were also sutured to the right ventricular epicardium as a precaution (in case atrial pacing failed to capture), but were not used. To depress its rate of spontaneous depolarization, the sinus node was modified by radiofrequency energy with an epicardial approach. This allowed control of the ventricular rate through atrial pacing while maintaining native atrioventricular conduction.

After calibration, a high fidelity 5 French pressure catheter (Millar Instruments, Houston, TX, U.S.A.) was introduced into the left atrium through its appendage. Likewise, to measure LV volumes and pressures, a calibrated 5 French 12-electrode conductance catheter (Millar Instruments) was advanced into the left ventricle by crossing the aortic valve. The latter catheter was connected to a dedicated system (Leycom®-CFL-512; Cardiodynamics BV, Argonstraat, The Netherlands) that continuously acquired and displayed pressure, volume and ECG signals. Proper positioning of the conductance catheter was guided by fluoroscopy and confirmed by the segmental volume signals.

In all animals, the catheter was placed along the long axis of the ventricle with its tip in the apex. Using fluoroscopic guidance, a pulmonary artery catheter (Swan-Ganz) was advanced from the right femoral vein to the pulmonary circulation. This catheter was used to measure cardiac output (CO) by thermodilution and to determine the parallel conductance effect with hypertonic saline injection.

Furthermore, to alter regional myocardial function, an arterial constrictor was placed around the left circumflex coronary artery and an ultrasonic flow transducer was placed distal to the arterial constriction. The inferior vena cava (IVC) was also dissected and a ring was placed around it to allow for gradual occlusion of the vein.

**Haemodynamic measurements**

To convert the conductance signals into volume data, the following three steps were taken. First, blood resistivity ($\rho$) was measured by connecting a Rho cuvette filled with 5 ml of blood to the CFL-512 system. Secondly, CO by both the conductance and pulmonary artery catheters was simultaneously acquired and the slope factor $\alpha$ calculated as: stroke volume (SV) by conductance catheter/SV by thermodilution. Parallel conductance was derived by injecting 10 ml of hypertonic saline into the pulmonary artery through the distal port of the thermodilution catheter. The CO measurements and saline injection were repeated 2–3 times.

All recordings of pressure and volume data were obtained at end-expiration. Minimal end-diastolic (EDP) and end-systolic (ESP) pressures were measured. LV volumes at end-diastole (EDV) and end-systole (ESV) and SV were obtained from the conductance catheter [8]. The first derivative of LV pressure in systole ($dP/dt$) and diastole ($-dP/dt$) and the time constant of LV relaxation (tau) were also derived [9]. A number of LV systolic function parameters were calculated using the pressure-volume loops, including end-systolic elastance ($E_{es}$, slope of ESP compared with ESV), the slope of $dP/dt$ against EDV and the preload recruitable stroke work (PRSW), derived as the slope of stroke work compared with EDV. LV stiffness was calculated as the difference between EDP and minimal pressure divided by SV. Left atrial ‘v’ wave pressure, early diastolic transmitral pressure gradient (TMG) and left atrial $dP/dt$ were also determined.

**Echocardiography**

The animals were imaged epicardially using a Sequoia ultrasound system (Acuson, Mountain View, CA, U.S.A.). Short-axis views were acquired to assess regional function in the lateral and the control segments (anteroseptal wall). Colour Doppler was applied to screen for mitral regurgitation both at baseline and with occlusion of the circumflex coronary artery. In the apical four-chamber view, the TD program was applied in pulsed-wave Doppler to record the mitral annular velocities at the septal and lateral areas. Gains and filters were adjusted to eliminate noise and allow a clear tissue signal. Peak $E_s$ and $A_s$ (intraobserver variability 5 ± 2%) at both areas of the annulus were measured under the different loading conditions, including presence and absence of ischaemia, and at the two pacing cycle lengths. The acceleration (AT, from onset to peak $E_s$) and deceleration (DT, by linear extrapolation of peak $E_s$ to baseline) times of $E_s$ at both areas were also determined (intraobserver variability 7 ± 2%). The time between the end of the annular descent during systole ($S_e$) and the onset of $E_s$ ($S_e - E_s$) was also measured (intraobserver variability 6 ± 3%).
Experimental protocol
We used a previous experimental design [10], and acquired data under two conditions: before and after the development of ischaemia, each at 450 and 550 ms. These R-R intervals were chosen to avoid merging of the annular velocities while still allowing the examination of the effect of cycle length on $E_a$ and $A_a$. All measurements were made at end-expiration. Throughout the experimental protocol, LV haemodynamics were allowed to equilibrate for 5–10 min before recording the changes. After acquiring baseline data, IVC occlusion was performed to decrease inflow and LV volumes and pressures, with subsequent reacquisition of haemodynamic and Doppler information at the new loading conditions. This was done at both the 450 and 550 ms cycle lengths.

Subsequently, we examined the effects of regional ischaemia on TD velocities by constricting the left circumflex coronary artery (Figure 1) until coronary artery blood flow decreased by ≥ 90 %. Again, Doppler velocities and haemodynamics were obtained to assess the effects of ischaemia. IVC occlusion was then repeated with simultaneous recording of TD velocities and haemodynamics. The ischaemia experiments were conducted at both cycle lengths.

Statistics
Two-way repeated measures ANOVA was applied to examine the effect of heart rate and ischaemia on the haemodynamic and TD measurements. For both haemodynamic and TD variables, data are shown as means ± S.E.M. Data are shown in the Tables for the different stages (i.e. baseline and ischaemia at each R-R interval). The statistical analysis is presented to show the effects of ischaemia irrespective of heart rate and likewise, the influence of heart rate irrespective of ischaemia. The presence of a significant interaction between the effects of ischaemia and heart rate on the haemodynamic and TD variables was also examined (interaction $P$ values in Tables 1 and 2). Regression analysis was used to correlate $E_a$ and $A_a$ values with the haemodynamic variables. Significance was present with $P \leq 0.05$.

RESULTS

Changes in regional function with ischaemia
At baseline, the thickening fraction in the lateral and septal segments was similar ($P > 0.4$); however, the lateral wall thickening fraction decreased significantly after induction of stenosis in the left circumflex coronary artery (from 33 ± 7 to 10 ± 4 %; $P < 0.01$), whereas a compensatory increase was noted in the systolic function of the septum (from 32 ± 5 to 41 ± 7 %; $P < 0.05$). The findings were similar at both the 450 and 550 ms cycle lengths. Of note, none of the ten animals developed mitral regurgitation.

Effect of ischaemia on LV systolic and diastolic function
The haemodynamic changes with ischaemia are shown in Table 1. LV filling pressures significantly increased ($P < 0.05$), whereas LV relaxation became worse (longer tau and decrease in LV $-dP/dt$; both $P < 0.05$). In addition, chamber stiffness was significantly greater with ischaemia ($P < 0.05$). Also, EDV and ESV increased significantly with coronary stenosis.

Global LV systolic function, assessed by $dP/dt$, $E_n$, slope of $dP/dt$ compared with EDV and PRSW, was significantly worse ($P < 0.05$). LV minimal pressure increased ($P < 0.05$) and the early diastolic transmitral pressure gradient became significantly lower ($P < 0.05$). These directional changes in global haemodynamics were noted at both cycle lengths.

Effect of ischaemia on mitral annular diastolic velocities
The changes with ischaemia in $E_a$ and $A_a$ at the lateral and septal areas are shown in Table 2. At the lateral area of the mitral annulus, ischaemia resulted in statistically significant decreases in $E_a$ and $A_a$ (Figure 2). However, non-significant trends for a prolongation in AT and DT of $E_a$ were present ($P > 0.1$). The time interval ($S_a - E_a$) became significantly longer ($P < 0.05$).

At the septal area, $E_a$ and $A_a$ decreased with ischaemia ($P = 0.04$). However, there were non-significant trends...
Effects of ischaemia and heart rate on LV systolic and diastolic functions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Ischaemia 450 ms</th>
<th>Baseline + 550 ms</th>
<th>450 ms + 550 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA 'v' wave pressure (mmHg)</td>
<td>10.6 ± 0.88</td>
<td>10.2 ± 0.88</td>
<td>10.1 ± 0.86</td>
<td>10.1 ± 0.86</td>
</tr>
<tr>
<td>LA dP/dt (mmHg/s)</td>
<td>130 ± 19</td>
<td>140 ± 20</td>
<td>144 ± 16.8</td>
<td>144 ± 15.2</td>
</tr>
<tr>
<td>LV EDP (mmHg)</td>
<td>6 ± 1.6</td>
<td>6 ± 1.6</td>
<td>6 ± 1.6</td>
<td>6 ± 1.6</td>
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<tr>
<td>Tau (ms)</td>
<td>40 ± 3.9</td>
<td>3.9 ± 5.9</td>
<td>7.9 ± 4.7</td>
<td>4.7 ± 3.3</td>
</tr>
<tr>
<td>dP/dt (mmHg/s)</td>
<td>1667 ± 64</td>
<td>1450 ± 24</td>
<td>1440 ± 24</td>
<td>1440 ± 24</td>
</tr>
<tr>
<td>Minimal pressure (mmHg)</td>
<td>1 ± 0.1</td>
<td>1 ± 0.1</td>
<td>1 ± 0.1</td>
<td>1 ± 0.1</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>60 ± 3.3</td>
<td>60 ± 3.3</td>
<td>60 ± 3.3</td>
<td>60 ± 3.3</td>
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<tr>
<td>LV dP/dt (mmHg/s)</td>
<td>183 ± 1159</td>
<td>130 ± 1819</td>
<td>120 ± 1665</td>
<td>120 ± 1665</td>
</tr>
<tr>
<td>E (mmHg/ml)</td>
<td>5.3 ± 0.75</td>
<td>5.3 ± 0.75</td>
<td>5.3 ± 0.75</td>
<td>5.3 ± 0.75</td>
</tr>
<tr>
<td>PRSW (mmHg)</td>
<td>65 ± 95</td>
<td>90 ± 57</td>
<td>80 ± 57</td>
<td>80 ± 57</td>
</tr>
</tbody>
</table>

For an increase in the AT and DT of Ea, the time interval (Sₐ - Eₐ) at the septal side was significantly prolonged (P = 0.017).

**Relationship of ischaemia-induced changes in Eₐ and Aₐ with LV haemodynamics**

A significant correlation was present between the percentage change in lateral Eₐ and the prolongation of tau (r = 0.76, P < 0.05; Figure 3). The correlation of Eₐ with tau was not significantly altered by the R-R interval. The change in Eₐ was also significantly related to the decrease in the TMG (r = 0.64, P < 0.05) and the increase in LV minimal pressure (r = −0.67, P < 0.05). The alterations in Eₑₑ (r = 0.7, P < 0.05), the slope of dP/dr against EDV (r = 0.72), PRSW (r = 0.65, P < 0.05) and regional systolic thickening (r = 0.67, P = 0.03) accounted for some of the changes in Eₐ. Using multiple regression analysis, changes in tau, TMG and the slope of dP/dr against EDV were the main determinants of the changes in lateral Eₐ (r = 0.87, R² = 0.76).

Regional (r = 0.75, P < 0.05) and global systolic function (slope of dP/dr against EDV; r = 0.67, P < 0.05) as well as tau (r = −0.73, P < 0.05) were the factors affecting the variance in septal Eₐ on multiple regression analysis (r = 0.82, R² = 0.67) (Figure 4).

**Prediction of LV filling pressures using the transmitral early diastolic velocity (E)/Eₐ ratio**

In the setting of acute ischaemia, significant correlations were present between left atrial 'v' wave pressure and the E/Eₐ ratio using either septal (r = 0.63, P < 0.05) or lateral (r = 0.65, P < 0.05) Eₐ. However, a stronger relationship was noted when the average of septal and lateral Eₐ was tested (r = 0.78, P < 0.05).

**Effect of cycle length on LV function**

Global and regional LV systolic function as well as chamber stiffness were similar at either cycle length (Table 1). However, tau, LV EDP and TMG significantly decreased at the shorter cycle length (P < 0.05).

**Effect of cycle length on Eₐ and Aₐ**

At the faster heart rate, Eₐ and Sₐ - Eₐ at both areas of the mitral annulus significantly decreased (P < 0.05; Table 2). In contrast, Aₐ significantly increased.

**Relationship of cycle length-induced changes in Eₐ and Aₐ with LV haemodynamics**

The decrease in lateral (r = 0.76, P < 0.05) and septal Eₐ (r = 0.68, P < 0.05) was significantly related to the decrease in the TMG (Figure 5). The shortening in Sₐ - Eₐ at both areas related significantly to the change in tau (lateral, r = 0.56; septal, r = 0.52; both P < 0.05), whereas...
Table 2  Effects of ischaemia and heart rate on mitral annulus diastolic velocities

<table>
<thead>
<tr>
<th>Parameters</th>
<th>550 ms</th>
<th>450 ms</th>
<th>Baseline + ischaemia</th>
<th>450 ms + 550 ms</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Ischaemia</td>
<td>Baseline</td>
<td>Ischaemia</td>
<td>550 ms</td>
</tr>
<tr>
<td>Lateral E_a (cm/s)</td>
<td>6.8 ± 0.45</td>
<td>5.3 ± 0.57</td>
<td>6.1 ± 0.45</td>
<td>4.0 ± 0.64</td>
<td>6.3 ± 0.32</td>
</tr>
<tr>
<td>Lateral S_a − E_a (ms)</td>
<td>87 ± 7.5</td>
<td>128 ± 12</td>
<td>68 ± 7.2</td>
<td>116 ± 6.8</td>
<td>110 ± 12</td>
</tr>
<tr>
<td>AT of lateral E_a (ms)</td>
<td>99 ± 7.9</td>
<td>124 ± 9.8</td>
<td>95 ± 5.3</td>
<td>114 ± 11.3</td>
<td>107 ± 11</td>
</tr>
<tr>
<td>DT of lateral E_a (ms)</td>
<td>137 ± 13.2</td>
<td>177 ± 9.4</td>
<td>128 ± 8.7</td>
<td>156 ± 8.7</td>
<td>157 ± 8</td>
</tr>
<tr>
<td>Lateral A_a (cm/s)</td>
<td>6.0 ± 0.8</td>
<td>5.6 ± 0.64</td>
<td>7.5 ± 0.49</td>
<td>6.7 ± 0.53</td>
<td>5.8 ± 0.42</td>
</tr>
<tr>
<td>Septal E_a (cm/s)</td>
<td>6.3 ± 0.37</td>
<td>5.7 ± 0.45</td>
<td>5.1 ± 0.79</td>
<td>4.7 ± 0.45</td>
<td>6 ± 0.23</td>
</tr>
<tr>
<td>Septal S_a − E_a (ms)</td>
<td>88 ± 6</td>
<td>114 ± 8.7</td>
<td>80 ± 7.5</td>
<td>103 ± 9</td>
<td>101 ± 6.1</td>
</tr>
<tr>
<td>AT of septal E_a (ms)</td>
<td>99 ± 11.3</td>
<td>112 ± 18</td>
<td>84 ± 12.7</td>
<td>100 ± 11.3</td>
<td>106 ± 7.5</td>
</tr>
<tr>
<td>DT of septal E_a (ms)</td>
<td>117 ± 14</td>
<td>143 ± 5</td>
<td>112 ± 6.4</td>
<td>130 ± 5</td>
<td>130 ± 7</td>
</tr>
<tr>
<td>Septal A_a (cm/s)</td>
<td>5.4 ± 0.68</td>
<td>4.8 ± 0.6</td>
<td>6.6 ± 0.53</td>
<td>5.6 ± 0.49</td>
<td>5.1 ± 0.4</td>
</tr>
</tbody>
</table>

Figure 2  TD imaging at the lateral area of the mitral annulus before and after ischaemia
E_a decreased from 9 to 6.5 cm/s. Note the increase in AT and DT and the prolongation of the S_a − E_a time interval from 113 to 139 ms.

Figure 3  Relationship between ischaemia-induced changes in lateral E_a and alterations in LV relaxation, transmitral pressure gradient and dP/dt against EDV
the decrease in LV EDP was related to the increase in Aa (lateral \( r = 0.69 \), septal \( r = 0.66 \), \( P < 0.05 \)).

**DISCUSSION**

The present study demonstrates that regional ischaemia results in reductions in ipsilateral and contralateral \( E_a \) values. In our model, changes in LV global and regional systolic and diastolic function accounted for the variance observed in lateral and septal \( E_a \). An important novel finding of the present study is the ability of the time interval \( S_a - E_a \) at both areas to detect changes in global LV diastolic function. In addition, in the setting of acute ischaemia, using the average of septal and lateral \( E_a \), as opposed to either velocity alone, in conjunction with the \( E_a \) results in a better prediction of left atrial pressure.

At the shorter cycle length, a significant decrease was observed in septal and lateral \( E_a \) along with a significant increase at both areas in Aa. These changes were related to the decrease in TMG and LV EDP respectively.

**Haemodynamic and TD changes with ischaemia**

Ischaemia resulted in worsening LV diastolic function, as reflected by the prolongation in tau and increases in LV minimal pressure and chamber stiffness. These findings are similar to those observed in previously reported regional ischaemia models with left anterior descending coronary artery (LAD) occlusion [10] and circumflex stenosis [11]. Likewise, these previous studies have shown a decline in regional systolic function with compensation from the non-ischaemic zones [11]. We have shown previously [7] that \( A_a \) is related directly to left atrial systolic function and inversely to left atrial afterload (LVEDP). Given the lack of change in left atrial dP/dt and the increase in LVEDP, \( A_a \) decreased with ischaemia.

Another important observation was the increase in the septal \( S_a - E_a \) time interval. Unlike peak velocity, the \( S_a - E_a \) time interval showed a more consistent response. \( A_a \) decreased significantly with ischaemia. We have shown previously [7] that \( A_a \) is related directly to left atrial systolic function and inversely to left atrial afterload (LVEDP). Given the lack of change in left atrial dP/dt and the increase in LVEDP, \( A_a \) decreased with ischaemia.

**Haemodynamic and TD changes with alterations in cycle length**

\( E_a \) at both areas of the mitral annulus decreased at the shorter cycle length. The change related well to the decrease in TMG. Interestingly, the time interval \( S_a - E_a \)
Effects of ischaemia and cycle length on annular velocities

Figure 5 Relationship between changes in TD velocities with tachycardia and haemodynamics
Upper panel, changes in $E_a$ compared with TMG pressure gradient. Lower panel, changes in $A_a$ compared with LVEDP.

at both areas became shorter at the higher heart rates. Although this may be due to the shorter cycle length, the observed changes were significantly correlated with those in tau. These results suggest that, in the setting of tachycardia, the measurement of this time interval may provide helpful insights into LV relaxation.

$A_a$ at both areas of the mitral annulus increased significantly at the shorter cycle length. Again, the haemodynamic changes in atrial afterload accounted well for these observations. With tachycardia, left atrial $dP/dt$ was unchanged, whereas LVEDP decreased significantly. Accordingly, $A_a$ increased with decreasing left atrial afterload.

Interestingly, $E_a$ and $A_a$ changes with tachycardia were similar to those reported previously [10] for the transmitral velocities.

Clinical implications
Our present results add important information regarding the application of TD velocities to the study of diastolic function in the setting of regional dysfunction and tachycardia. Specifically, in the setting of regional dysfunction, both septal and lateral $E_a$ should be examined when drawing inferences about LV relaxation. For example, when lateral dysfunction is present, lateral $E_a$ is reduced, whereas septal $E_a$ may not be altered. Conversely, in a patient with septal dysfunction and a hyperdynamic lateral wall, lateral $E_a$ may be normal or increased despite the presence of global LV diastolic dysfunction. Accordingly, as shown in the present study, in patients with regional dysfunction, the average $E_a$ should be used in conjunction with $E$ to allow for an accurate prediction of LV filling pressures. Furthermore, a novel and important finding of the present study is the prolongation of the time interval $S_a - E_a$ at the septal and lateral areas in the stages with impaired relaxation. Unlike peak velocities, the septal and lateral time intervals were more frequently concordant when regional dysfunction was present.

With respect to the effects of tachycardia in normal ventricles, a reduced $E_a$ should not be used to infer an abnormality in LV diastolic function. As noted in the present study, alterations in $E_a$ were primarily due to a decrease in TMG. With faster heart rates in the setting of impaired relaxation, however, $E_a$ still provides a reasonable assessment of LV diastolic function, since the correlation of $E_a$ with tau was not significantly altered by the R-R interval. In addition to these experimental observations in the setting of impaired relaxation, previous clinical studies [12,13] have reported the use of $E/E_a$ ratio for the prediction of filling pressures in the presence of sinus tachycardia.

Limitations
In the present study, we did not include an LAD occlusion in the protocol. Accordingly, we did not examine the effect of septal ischaemia on annular velocities. However, our objective was to study the effect of ischaemia itself and not to induce ischaemic changes in each vascular territory. Besides, the addition of an LAD occlusion, following the circumflex stenosis, to the same protocol would have resulted in an exceptionally long time that would have jeopardized the successful execution of these experiments. We measured only lateral and septal velocities and, therefore, we are unable to address the role of anterior and inferior $E_a$ and whether they add additional accuracy over the average of only septal and lateral velocities.

We examined only two cycle lengths acutely. The R-R intervals were chosen to avoid merging of $E_a$ and $A_a$ at the faster heart rates. Therefore the present study cannot address clinical settings when actual complete merging is present. Also, the effect of chronic tachycardia cannot be addressed from these experiments, as the animals were
studied with the pericardium open. However, we were interested in evaluating the changes of TD velocities in response to ischaemia and alterations in cycle length. Accordingly, whatever influence the open pericardium has on TD velocities, its effect was present throughout all the experimental stages and thus cancels out when changes are examined.

Finally, we have shown significant correlations between several haemodynamic measurements and Doppler velocities. Although the correlations do not prove causality, the consistency of the observations and the ability of the multiple regression models to account for most of the variance in annular velocities support the impact of the changes in LV function as determined invasively on Ea and Aa.

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REFERENCES