Noninvasive Assessment of Left Ventricular Force-Frequency Relationships Using Tissue Doppler–Derived Isovolumic Acceleration Validation in an Animal Model

Michael Vogel, MD, PhD; Michael M.H. Cheung, MB, ChB, MRCP; Jia Li, MD; Steen B. Kristiansen, MD; Michael R. Schmidt, MD; Paul A. White, PhD; Keld Sorensen, MD; Andrew N. Redington, MD, FRCP

Background—We have demonstrated that myocardial acceleration during isovolumic contraction (IVA) is a sensitive index of right ventricular contractile function. In this study, we assessed the usefulness of IVA to measure left ventricular (LV) contractile function and force-frequency relationships in an experimental preparation.

Methods and Results—In study 1, we examined 6 pigs by use of tissue Doppler imaging of LV free wall and simultaneous measurements of intraventricular pressure, volume, maximal elastance (Emax), and dP/dt max by conductance catheterization. Animals were paced via the right atrium at a rate of 130 bpm. IVA was compared with elastance during contractility modulation by esmolol and dobutamine and assessed during preload reduction and afterload increase. In study 2, in 6 more pigs, force-frequency data were obtained during incremental atrial pacing from 120 to 180 bpm. Study 1: Esmolol led to a decrease in IVA and Emax (P<0.03 and <0.02, respectively), both of which increased during dobutamine infusion (P<0.02 and <0.03, respectively). IVA was unaffected by significant (P<0.001) acute reduction of LV volume and a significantly increased LV afterload (systolic pressure increase, P<0.001). Study 2: There was a positive correlation between IVA and dP/dt max (r²=0.92, P<0.05). As heart rate was increased from 120 to 160 bpm, there were significant increases in both IVA and dP/dt max (P<0.0004 and P=0.02, respectively). Over the same range of heart rates, there was no significant change in Emax (P=0.22).

Conclusions—IVA is a measurement of LV contractile function that is unaffected by preload and afterload changes within a physiological range and can be used noninvasively to measure LV force-frequency relationships. (Circulation. 2003;107:1647-1652.)

Key Words: contractility ■ echocardiography ■ ventricle

Tissue Doppler echocardiography (TDE) has emerged as a useful tool to quantify regional left ventricular (LV) function. Attempts to describe global ventricular contractile function from systolic myocardial velocities have yielded promising results, but, as with many other single-beat ejection-phase indices, their usefulness is limited by both preload and afterload dependency. We have recently shown that myocardial acceleration during isovolumic contraction (IVA) derived from TDE is a robust measurement of right ventricular contractile function. In our experiments, we found that IVA was sensitive to small changes in inotropy but unaffected by large changes in right ventricular preload and afterload. We hypothesized that, in a similar way, myocardial acceleration during isovolumic contraction (IVA) may reflect LV myocardial contractile function. Furthermore, although we were able to show that myocardial acceleration could describe the force-frequency relationship in the right ventricle, no noninvasive index has been used previously in the LV in either an experimental or clinical setting. Thus, we first validated the usefulness of IVA as a load-independent index of contractility (study 1) and also assessed the ability of IVA to describe the force-frequency relationship during incremental atrial pacing in pigs (study 2).

Methods

Tissue Doppler Echocardiography

Transthoracic echocardiography was performed in all studies using the System V ultrasound scanner (GE Vingmed). In a 4-chamber equivalent view, the LV free wall was imaged, and color-coded myocardial velocities were recorded at the base immediately (0.5
cm) below the insertion of the posterior mitral valve leaflet. Imaging parameters were optimized to achieve the highest possible frame rate. Pulse repetition frequency was set at the lowest possible value without aliasing. Recordings were made simultaneously with ECG. A cine loop of at least 6 consecutive cardiac cycles was stored digitally for offline analysis.

**Study 1: Validation of IVA**

We studied 15-kg Danish Landrace pigs (Paaskehojgaardcentret, Trige, Denmark). The study conformed to the guidelines of the American Heart Association on research animal experiments. Our protocol has been described in detail previously. After premedication with azaperone (4 mg/kg IV), midazolam (0.1 mg/kg IV), and etomidate (0.5 mg/kg IV), the animals were endotracheally intubated and ventilated with a Servo 900 (Siemens) ventilator. Arterial blood gases were taken to confirm adequate ventilation during the study. Anesthesia was maintained with isoflurane 2% in a mixture of NO2 and oxygen. Via the right carotid artery, a custom-made 8-polar 5F combination conductance-pressure catheter (Millar Instruments) was placed into the apex of the LV under fluoroscopic guidance. The micromanometer pressure transducer output was fed to a custom-built amplifier. The conductance catheter was connected to a signal-processing unit (Sigma 5DF, Cardiodynamics Corp). A 20-mm latex balloon catheter was placed via the right external jugular vein at the junction of the inferior vena cava and the right atrium and subsequently inflated to modify preload. Via the left carotid artery, a Rashkind balloon septostomy catheter (Medtec) was placed in the descending aorta and prepared for inflation to modify LV afterload. Via the right external jugular vein, a standard 5F thermodilution catheter (Baxter Healthcare) connected to a dedicated cardiac output processing computer (Com2, Baxter Edwards) was placed in the main pulmonary artery. A 5F pacing wire was inserted into the left external jugular vein, advanced into the right atrium, and connected to an external pacemaker generator (Medtronic). The right atrium was paced at a constant rate of 130 bpm during preload and afterload changes and during contractility modulation. Pressure and volume data were digitized at 1000 Hz and stored on a personal computer with dedicated software for later analysis. Parallel conductance was calculated in the usual way after injection of 2 mL of 10% NaCl into the inferior vena cava. The gain constant α was calculated as the ratio of conductance-derived stroke volume, and the stroke volume was measured by thermodilution.

**Study 2: Experimental Measurement of Force-Frequency Relationships**

For logistical reasons, the experimental preparation was different from that of study 1. We used 15-kg Yorkshire pigs that were premedicated with midazolam 0.3 mg/kg and acepromazine 3 mg/kg. Anesthesia and instrumentation of the animals were essentially the same as in study 1 except for the insertion of the aortic occlusion balloon.

**Protocol**

**Study 1**

All physiological data were obtained during apnea to minimize cardiopulmonary interactions. Echocardiography and pressure-volume data were recorded simultaneously, and cardiac output was measured at each stage. The measurements were obtained during the following protocol, chronologically: (1) baseline; (2) preload reduction (inferior caval balloon occlusion) with simultaneous measurement of beat-to-beat changes in LV pressure and volume and TDE indices; (3) afterload increase (descending aortic balloon occlusion) with the same measurements as for preload reduction; and (4) change in inotropy.

First, 500 μg · kg⁻¹ · min⁻¹ of esmolol was infused for 5 minutes and increased to 1 mg · kg⁻¹ · min⁻¹ for 5 minutes more. After a 10-minute washout period, dobutamine was infused at a rate of 10 μg · kg⁻¹ · min⁻¹ for 10 minutes. Conductance catheter-derived pressure-volume data were obtained during transient preload reduction by balloon occlusion at steady state to obtain a family of pressure-volume loops before commencement of each drug and after stabilization at each dose. TDE data were also recorded immediately before each conductance catheter measurement.

**Study 2: Force-Frequency Relationship**

Recordings were obtained as in study 1. In this study, the basal pacemaker rate was set at 120 bpm for 1 minute and increased by increments of 20 bpm to a maximum rate of 180 bpm or whenever atrioventricular block or mechanical alternans was induced. At each increment, TDE data, ventricular pressure recordings, and a family of pressure-volume loops were obtained.

**Data Analysis**

Pressure-volume data were analyzed offline by examiners (P.W., M.C.) blinded to the data obtained by TDE, which were analyzed by a different observer (M.V.). All conductance volumes were corrected for parallel conductance and the gain constant α. The maximal slope (left upper shoulder) of the end-systolic pressure-volume relation, maximal elastance (Emax) during caval occlusion, and dP/dtmax were calculated. Echopac software (GE Vingmed) was used to analyze the stored TDE data by our previously described method. The sample volume (1×1 pixel) was placed in the middle of the myocardium at the basal free wall (Figure 1). The resulting tissue velocity traces were displayed and
analyzed by use of commercially available software (Echopac). Data points were smoothed with a 3-point moving average filter. Peak myocardial velocities during isovolumic contraction, systolic ejection (s wave), and acceleration during isovolumic contraction were measured with electronic calipers. Acceleration was calculated as the difference between baseline and peak velocity divided by their time interval.3 Display of the TDE data within the analysis package was optimized by maximizing the width of the individual beat to minimize measurement error.

For steady-state conditions, measurements of myocardial acceleration and velocities were calculated from 3 consecutive cardiac cycles, with the average of the 3 measurements recorded. A second independent observer (M.R.S.), who was blinded to the results of the TDE-derived data analysis, measured IVA in 50 data sets to assess interobserver variability, and the first observer (M.V.) remeasured these 50 data sets on a different day to assess intraobserver variability. Individual, sequential beat-to-beat comparison of myocardial velocities during isovolumic contraction, systolic ejection (s wave), and acceleration during isovolumic contraction were measured with electronic calipers. Acceleration was calculated as the difference between baseline and peak velocity divided by their time interval.3 Display of the TDE data within the analysis package was optimized by maximizing the width of the individual beat to minimize measurement error.

**Statistical Analysis**

Data are expressed as mean±SD.

Study 1: Measurements of TDE-derived parameters and pressure-volume data during changes in loading conditions were analyzed by ANOVA for repeated measurements. Linear regression analysis was used to compare changes in E\textsubscript{max} with changes in IVA and isovolumic contraction myocardial velocity. Student’s t test for paired values was used to compare the changes in indices with modulation of contractility with dobutamine and esmolol. Bland-Altman analysis5 was performed to assess interobserver variability.

Study 2: Linear regression analysis was used to assess pacing-induced changes in dP/dt\textsubscript{max}, E\textsubscript{max}, and IVA between heart rates of 120 to 180 bpm. Student’s t test for paired values was used to compare changes in dP/dt\textsubscript{max}, E\textsubscript{max}, and IVA between 120 and 160 bpm.

**Results**

**Intraobserver and Interobserver Variability**

We found a 9.8±7.8% (0% to 25.1%) interobserver variability and a 5.7±4.6% (0% to 14.9%) intraobserver variability of measurements of IVA. Bland-Altman analysis of interobserver variability shows 47 of 50 data points lying within 2 SD of the difference in observed values (Figure 2).

Study 1: TDE data were acquired with a frame rate between 131 and 248 frames per second (median, 178), the pulse repetition frequency ranged from 0.5 to 1.5 kHz, and the Nyquist limit ranged from 14 to 42 cm/s. Six animals were studied. IVA occurred very early during LV contraction, starting at or just before the timing of mitral valve closure and coinciding with early LV pressure rise (Figure 1). Furthermore, an instantaneous plot of IVA versus dP/dt\textsubscript{max} (Figure 3) showed peak IVA occurring well before the timing of peak dP/dt. During preload reduction, there was a decrease in LV end-diastolic volume by 9.9±3.2% (5.1% to 15.1%) (P<0.0001), and during afterload increase, LV pressure increased by 30±11.9% (20.1% to 47.2%) (P<0.0002). IVA was unaffected by this preload and afterload modification, whereas dP/dt\textsubscript{max} and systolic myocardial velocities changed significantly beat-by-beat during these maneuvers (Table 1).

The data regarding contractile change are given in Table 2. There was a significant increase in IVA during dobutamine infusion (P<0.02) and a reduction with esmolol (P<0.03) (Figure 4). The changes in contractile state with dobutamine and esmolol were also reflected by significant changes in E\textsubscript{max} (P<0.03 and P<0.02, respectively). There was, however, a >100% change in the value of IVA with modulation of contractility, whereas the change in the value of E\textsubscript{max} was between 30% and 50% (Table 2).

Study 2: Frame rates for TDE data acquisition ranged from 149 to 208 frames per second (median, 185), the pulse repetition frequency ranged from 0.5 to 1.5 kHz, and the Nyquist limit ranged from 14 to 42 cm/s. In 4 of the 6 animals studied, the peak HR achieved was 160 bpm, and a peak HR of 180 bpm was achieved in the other 2. The development of mechanical alternans, detectable from pressure-volume analysis and IVA, was responsible for terminating the study in all animals. There was a positive correlation between IVA and dP/dt\textsubscript{max} and also between IVA and heart rate (r²=0.92, P<0.05, and r²=0.99, P<0.004, respectively). Although E\textsubscript{max} was also positively correlated with heart rate, this relationship did not reach significance (r²=0.76, P=0.13). Overall IVA increased from 3.8±1.4 to 9.1±2.3 m/s² (P<0.0004, n=6) as heart rate increased from 120 to 160 bpm (Table 3). Simultaneously measured dP/dt\textsubscript{max} increased from 1150±113 to 1249±82 mm Hg/s over the same range of heart rates (P=0.02, n=6). Although maximum elastance also showed a positive correlation with basal IVA (r²=0.70), the change in elastance from 120 to 160 bpm did not reach significance (P=0.22).

**Discussion**

Our data show that IVA is a useful new TDE-derived tool to evaluate LV contractile function. Our experimental studies have confirmed that it is resistant to physiological changes in...
changes of preload and afterload, and we validated its usefulness in measurement of force-frequency relationships.

The definition and measurement of LV contractility remain difficult and, to a large extent, elusive. Isometric, length-tension, and force-frequency methods all have merits but measure different aspects of LV contractile function. The ideal index of LV contractile function for clinical use should be sensitive to changes in isotropic state, independent of load changes in the physiological range, and obtainable noninvasively. Although obviously limited by its invasive nature, assessment of systolic elastance, despite being less sensitive to contractile change than some indices (e.g., dp/dt_{max}), has become the “gold standard” of contractility measurement because of its relative resistance to load changes. In this study, data derived by conductance catheter were compared with isovolumic and ejection-phase indices obtained noninvasively by TDE. Our data demonstrated that IVA reflected changes in systolic elastance, varying appropriately with myocardial contractile state. Imposed contractile change during esmolol and dobutamine infusion led to an ≈30% to 50% change in E_{max} but a 100% change in IVA, perhaps reflecting the greater sensitivity of IVA over E_{max} in detecting changes in contractility. Furthermore, IVA and, as expected, E_{max} were unaffected by statistically and physiologically significant changes of preload and afterload that had adverse effects on ejection-phase velocities and dp/dt_{max}.

Thus, our data confirm those of Oki et al and demonstrate a load dependency of ejection-phase myocardial velocities independent of heart rate. More complex tissue Doppler derivations, eg, myocardial strain rate, have not been tested for load dependency but are likely to be affected similarly. This overtly limited usefulness of TDE-derived single-beat ejection-phase indices is consistent with the known limitations of similar indices, such as ejection fraction, velocity of circumferential fiber shortening, and more complex derivations such as the velocity of circumferential fiber shortening–end-systolic wall stress relation.

### Load-Independence of IVA
IVA begins at the very onset of LV pressure rise. As such, it represents the earliest of systolic events, and this may explain why it is more robust, in terms of its load dependency, than other isovolumic indices. By the method used in this study, IVA is a measurement of the average rate of acceleration early during isovolumic contraction. This method of calculation was chosen pragmatically to reflect the currently available software and hardware. However, manipulation of the data offline to produce the first derivative of the myocardial velocity curve (dVel/dt, Figure 3) showed peak dVel/dt to occur substan-

<table>
<thead>
<tr>
<th>TABLE 1. Effect of Preload Reduction and Afterload Increase Measured by Conductance Catheter and Simultaneous TDE Data During 7 Consecutive Cardiac Cycles</th>
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<tbody>
<tr>
<td>Cycle 1</td>
</tr>
<tr>
<td>Preload reduction</td>
</tr>
<tr>
<td>IVA, m/s²</td>
</tr>
<tr>
<td>IVV, cm/s</td>
</tr>
<tr>
<td>s-Wave acc, m/s²</td>
</tr>
<tr>
<td>LVEDV, mL</td>
</tr>
<tr>
<td>Max dp/dt, mm Hg/s</td>
</tr>
<tr>
<td>Afterload increase</td>
</tr>
<tr>
<td>IVA, m/s²</td>
</tr>
<tr>
<td>IVV, cm/s</td>
</tr>
<tr>
<td>s-Wave acc, m/s²</td>
</tr>
<tr>
<td>LVEDV, mL</td>
</tr>
<tr>
<td>Max dp/dt, mm Hg/s</td>
</tr>
</tbody>
</table>

IVA indicates isovolumic velocity; acc, acceleration; and LVEDV, LV end-diastolic volume.

<table>
<thead>
<tr>
<th>TABLE 2. Simultaneous Assessment of Contractile Function by Conductance Catheter and TDE at Rest and During Esmolol and Dobutamine Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esmolol (1000 µg · kg⁻¹ · min⁻¹)</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
</tr>
<tr>
<td>E_{max}, mm Hg/mL</td>
</tr>
<tr>
<td>IVA, m/s²</td>
</tr>
<tr>
<td>IVV, cm/s</td>
</tr>
<tr>
<td>s-Wave acceleration, m/s²</td>
</tr>
<tr>
<td>s-Wave velocity, cm/s</td>
</tr>
</tbody>
</table>

Thus, our data confirm those of Oki et al and demonstrate a load dependency of ejection-phase myocardial velocities independent of heart rate. More complex tissue Doppler derivations, eg, myocardial strain rate, have not been tested for load dependency but are likely to be affected similarly. This overtly limited usefulness of TDE-derived single-beat ejection-phase indices is consistent with the known limitations of similar indices, such as ejection fraction, velocity of circumferential fiber shortening, end-systolic wall stress relation.
tially earlier than \( \frac{dP}{dt_{\text{max}}} \). The rate of change of myocardial velocity begins to decline well before the time of peak intracavitary \( \frac{dP}{dt_{\text{max}}} \), the latter of which is well known to be sensitive to changes in load.\(^8\) TDE-derived myocardial velocities during isovolumic contraction have been measured in earlier animal studies. The peak myocardial posterior wall velocity during isovolumic contraction, measured in short-axis section, correlated with M-mode–derived ejection fraction changes during dobutamine infusion in one study.\(^14\) However, the lack of further pharmacological manipulation or load variation and the use of ejection fraction as the independent index of contractility make these data difficult to interpret. In our study, the peak long-axis velocity during isovolumic contraction was sensitive to changes in contractility during dobutamine infusion and with changes in heart rate, but it was unable to detect decreased contractility induced by esmolol and, unlike IVA, was significantly altered by increased afterload.

The effect of our loading maneuvers and their limitations warrant further discussion. Although the absolute change in LV volume during preload reduction was relatively modest, it was a highly statistically significant change, which led to statistically significant differences in other parameters, whereas IVA was unaffected. Furthermore, the range of change was much larger than the stated mean change. There are remarkably few in vivo studies that give absolute numbers for the amount of change in preload that was imposed during validation of the index being examined. The extent of the changes in our study are comparable to those published for similar in vivo validation studies performed in experimental preparations\(^15\) and human subjects.\(^12,13\)

However, as with all indices purporting to measure intrinsic contractile function, the limitations of IVA, although fewer than many, must be taken into account in any subsequent studies using this index. Nonetheless, the feasibility to easily and noninvasively describe RV\(^5\) and LV contractile function and instantaneous force-frequency relationships makes IVA particularly attractive for clinical and experimental studies of transient hemodynamic changes in the individual and may greatly enhance our ability to measure myocardial performance in the uninstrumented in vivo heart.

**Assessment of the Force-Frequency Relation**

Another important reflection of LV contractile state is the force-frequency relationship.\(^16\) This function is frequently measured by use of isometric twitch velocities in vitro\(^16,17\) and \( \frac{dP}{dt_{\text{max}}} \) in vivo.\(^18\) Interestingly, in a recent study, neither strain nor strain rate, by use of TDE, was sensitive to the change in heart rate, whereas both varied appropriately with changes in inotropy.\(^19\) The effects of load were not directly examined in the study, but the authors speculated that the expected increase in contractility may have been offset by the reduced preload imposed by tachycardia. Our study shows that the force-frequency relationship can be measured by use of IVA, supporting its relative load independence. In vitro, attenuated force-frequency relationships have been demonstrated in the myocardium of patients with dilated cardiomyopathy and congestive heart failure secondary to chronic mitral incompetence.\(^20\)

**Table 3. Changes in Indices of LV Contractile Function With Pacing**

<table>
<thead>
<tr>
<th>Heart Rate (n)</th>
<th>IVA, m/s(^2)</th>
<th>IVV, cm/s</th>
<th>s-Wave Velocity, cm/s</th>
<th>Max ( \frac{dP}{dt_{\text{max}}} ), mm Hg/s</th>
<th>( E_{\text{max}} ), mm Hg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>120 (6)</td>
<td>3.8±1.4</td>
<td>5.0±1.9</td>
<td>7.2±3.0</td>
<td>1150±113</td>
<td>1.6±0.7</td>
</tr>
<tr>
<td>140 (6)</td>
<td>6.3±1.3</td>
<td>8.2±2.2</td>
<td>8.3±4.0</td>
<td>1219±73</td>
<td>2.1±1.7</td>
</tr>
<tr>
<td>160 (6)</td>
<td>9.1±2.3</td>
<td>10.2±2.8</td>
<td>9.0±5.3</td>
<td>1249±82</td>
<td>2.2±1.5</td>
</tr>
<tr>
<td>180 (2)</td>
<td>12.8±1.0</td>
<td>10.6±1</td>
<td>9.2±3.5</td>
<td>1280±141</td>
<td>2.2±0.8</td>
</tr>
</tbody>
</table>
To date, the in vivo description of LV force-frequency relationships has required invasive measurements for its derivation. Our experimental study showed a highly significant increase in IVA with increased heart rate and a good correlation between IVA and dP/dt max during incremental tachycardia. Interestingly the correlation between IVA and E max was less marked and the overall change in E max was insignificant, perhaps reflecting the relative lack of sensitivity of elastance to contractile change. It is worthy of note that in the original description of the usefulness of E max as an index of contractility, increases in heart rate through pacing had no effect on E max.

Potential Clinical Application

The relationship between heart rate and cardiac output is a complex one, particularly in the complex hemodynamic milieu of ischemic and idiopathic dilated cardiomyopathy and preoperative or postoperative congenital heart disease. However, better understanding of the force-frequency relationship may explain some of the unpredictability of responses to bradycardia and tachycardia in such patients and potentially could guide management by optimizing heart rate, contractility, and inotropic therapy. More data are required before the usefulness of measurements of the force-frequency relationship in the clinical setting can be assessed in detail. None-the-less, because the derivation of IVA requires very little offline analysis (no more than a calculation of fractional shortening, for example), IVA has the potential to be used at the bedside to monitor hemodynamic change either in ambulatory patients (using indwelling pacemaker systems or trans-esophageal atrial pacing) or in the intensive care unit, where temporary epicardial pacing wires are frequently used.

Limitations

Measurement of IVA has become possible because of the high frame rate and rapid digital data acquisition achieved by currently available ultrasound technology. Duration of IVA is in the range of 10 to 40 ms; thus, even with the very high frame rates used in our study (130 to 250 frames per second), data were acquired only every 4.0 to 7.6 ms, ie, 2 to 10 frames were acquired during IVA. This does allow measurement of IVA; however, improvements in sampling rate will be necessary to increase the accuracy of this assessment. It is unlikely, particularly because other indices demonstrated significant changes, that we failed to demonstrate a real change with loading variation, but clearly further software and hardware developments will be necessary to maximize and standardize frame rates to reduce error. Careful attention to machine setup is required pending such developments.

Conclusions

IVA is a novel, easily obtained, noninvasive index of LV contractile state that is unaffected by physiological changes in preload and afterload. The ability to detect changes with the force-frequency relationship and during pharmacological manipulation makes this a potentially attractive method for clinical and experimental evaluation of systolic cardiac function in vivo.

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