Validation of Myocardial Acceleration During Isovolumic Contraction as a Novel Noninvasive Index of Right Ventricular Contractility

Comparison With Ventricular Pressure-Volume Relations in an Animal Model

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Background—We have demonstrated that myocardial acceleration during isovolumic contraction (IVA) is a sensitive index of left ventricular contractile function. In this study, we assessed the utility of IVA to measure right ventricular (RV) contractile function.

Methods and Results—We examined 8 pigs by using tissue Doppler imaging of the RV free wall and simultaneous measurements of intraventricular pressure, volume, maximal elastance (e_{max}), preload recruitable stroke work, and dP/dt_{max} by conductance catheterization. Animals were paced in the right atrium at a rate of 130 beats per minute (bpm). IVA was compared with elastance during contractility modulation by esmolol and dobutamine and during preload reduction and afterload increase by transient balloon occlusion of the inferior vena cava and pulmonary artery, respectively. Data were also obtained during incremental atrial pacing from 110 to 210 bpm. Esmolol led to a decrease in IVA and dP/dt_{max}. During dobutamine infusion, IVA, dP/dt_{max}, preload recruitable stroke work, and e_{max} all increased significantly. During preload reduction and afterload increase, IVA remained constant up to a reduction of RV volume by 54% and an RV systolic pressure increase of 58%. Pacing up to a rate of 190 bpm led to a stepwise increase in IVA and dP/dt_{max}, with a subsequent fall at a pacing rate of 210 bpm.

Conclusions—IVA is a measurement of RV contractile function that is unaffected by preload and afterload changes in a physiological range and is able to measure the force-frequency relation. This novel index may be ideally suited to the assessment of acute changes of RV function in clinical studies. (Circulation. 2002;105:1693-1699.)

Key Words: ventricles ■ pacing ■ contractility ■ echocardiography

In recent years there has been an increased interest in the assessment of right ventricular (RV) function in both acquired and congenital heart disease.1–3 Because of its complex geometric shape and other spatial considerations, it has been notoriously difficult to noninvasively assess RV function.4 Although RV ejection fraction can now be derived from volumetric data obtained by MRI or 3-dimensional echocardiography, the load dependency of ejection fraction limits its utility.5,6 Indeed, validity of any single beat–derived ejection phase index of RV contractile function is questionable because changes in loading conditions, especially afterload, markedly influence such measurements. Furthermore, the RV in congenital heart disease is frequently characterized by pressure or volume overload, obviating useful comparison of these ejection phase indexes with data derived in the normal RV.1 Tissue Doppler imaging (TDI) has the potential to assess ventricular contractile function independent of the shape of the ventricle. However, the magnitude of ejection phase myocardial velocities has been shown to be preload and afterload dependent.6 Isovolumic indexes are likely to be more robust. Indeed, isometric myocardial twitch velocities are frequently used in in vitro studies of myocardial contractile function.7,8 Myocardial velocities, recorded in vivo, during isovolumic contraction have also been studied through the use of TDI.9 In an animal study there was an acceptable (r=0.72) correlation between peak velocity during isovolumic contraction and ejection fraction, but neither load nor heart rate dependency was formally assessed.9 Myocardial acceleration has not been measured previously through the use of TDI; however, with the use of a microaccelerometer sensor located in the tip of a pacing lead developed with the intention to optimize pacing systems,10 experimental and
clinical studies have demonstrated that peak endocardial acceleration occurs during isovolumic contraction and increases linearly during dobutamine infusion. Recently, we demonstrated using TDI in an animal model that myocardial acceleration during isovolumic contraction (IVA) is a relatively load-independent index of left ventricular (LV) contractile function. The hypothesis of this study was that IVA would be a similarly robust index of contractile function in the RV. We compared IVA with other TDI-derived indexes of systolic function and the “gold” standard of invasive assessment of contractile function, the analysis of pressure-volume relations in a closed-chest animal model during modulation of preload, afterload, contractility, and heart rate.

Methods

Animal Protocol
We studied 8 Danish land-race pigs weighing ~15 kg. The study conformed to the guidelines of the American Heart Association on research animal experiments. After premedication with azaperone (4 mg/kg), midazolam (0.1 mg/kg), 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 2% isofluorane in a mixture of NO2 and oxygen. A cutdown was performed on both sides of the neck. Through the right internal jugular vein, a custom-made 8 polar (total interelectrode distance, 3 cm), SF combination conductance-pressure catheter (Millar Instruments) was placed into the apex of the RV under fluoroscopic guidance. The micromanometer pressure transducer output was fed to a custom-built amplifier. The conductance electrodes were connected to a signal-processing unit (Sigma SDF, Cardiodynamics Corp.). A 20-mm latex balloon catheter (Boston Scientific) was placed into the right internal jugular vein at the junction of the inferior vena cava and the right atrium and subsequently inflated to modify preload. Through the left internal jugular vein, a Rashkind balloon septostomy catheter (Meditec) was placed in the main pulmonary artery and prepared for inflation to modify RV afterload. After modification of loading conditions, the balloon catheter in the pulmonary artery was removed and replaced by a standard 7F thermodilution catheter (Baxter Healthcare) connected to a dedicated cardiac output processing computer (Com2, Baxter Edwards). A SF 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 beats per minute (bpm) during preload and afterload changes during partial occlusion of the inferior vena cava. The gain constant α was calculated as the ratio of conductance-derived stroke volume and the stroke volume measured by thermodilution.

Transthoracic echocardiography was performed with the use of a GE Vingmed Vivid V ultrasound scanner with a frame rate between 131 and 248 Hertz. In a 4-chamber equivalent view, the RV free wall was imaged and color-coded myocardial velocities were recorded at the base immediately below the insertion of the tricuspid valve leaflets. Recordings were made simultaneously with ECG. A cineloop of at least 6 consecutive heartbeats was stored digitally for off-line analysis.

Protocol
All physiological data were obtained during apnea to minimize cardiopulmonary interactions. Echocardiography and pressure-volume data were simultaneously recorded, and at each stage cardiac output was measured.

The measurements were obtained during the following protocol, chronologically:

1. Baseline
Baseline measurements were performed first.

2. Preload Reduction
To assess the effect of preload reduction on IVA, TDI was performed continuously during partial occlusion of the inferior vena cava, and a cineloop of 6 consecutive cardiac cycles at different stages of ventricular volume was recorded. An electrical timing signal was recorded to synchronize TDI and pressure and volume data during balloon inflation.

3. Afterload Increase
After a 10-minute rest period, a balloon was inflated in the pulmonary artery until RV systolic pressure had increased by at least 25%. TDI and RV pressure data were recorded simultaneously.

4. Heart Rate Modulation
The pacemaker rate, which otherwise was kept constant at 130 bpm, was reduced to 110 for 1 minute and rapidly increased by increments of 10 bpm to a maximum rate of 210 bpm. At each increment, TDI data and ventricular pressure recordings were obtained.

5. Reduced Contractility
After a further 10-minute rest period, an infusion of 500 μg/kg per minute of esmolol started, which was increased to 1 mg/kg per minute after 5 minutes and maintained at the latter level for a further 5 minutes. Conductance catheter-derived pressure-volume data were obtained during transient preload reduction by balloon occlusion at steady state before commencing esmolol and at each dosage increment. TDI data were also recorded immediately before each conductance catheter measurement.

6. Increased Contractility
After a further 10-minute rest, dobutamine was infused at a rate of 10 μg/kg per minute for 10 minutes. Conductance catheter-derived pressure-volume data were obtained during transient preload reduction by balloon occlusion at steady state before commencing dobutamine and after dobutamine had been administered for at least 10 minutes. TDI data were also recorded immediately after each conductance catheter measurement.

Data Analysis
Pressure-volume data were analyzed off-line by one examiner who was blinded to the data obtained by TDI, which were analyzed by a different observer. All conductance volumes were corrected for parallel conductance and the gain constant α. The maximal slope (maximal P/V) of the end-systolic pressure-volume relation: end-systolic elastance (eSV) during caval occlusion, preload recruitable stroke work (PRSW), and dP/dt max were calculated. Echocardiographic software (GE Vingmed) was used to analyze the stored TDI data. The sample volume was placed in the middle of the myocardium at the basal free wall. Peak myocardial velocities during isovolumic contraction (Q wave to onset of systolic ejection), systolic ejection (S wave), as well as acceleration during isovolumic contraction were recorded (Figure 1). Acceleration was calculated as the difference between baseline and peak velocity divided by their time interval. Measurements of myocardial acceleration and velocities were calculated from 3 consecutive cardiac cycles with the average of the 3 measurements recorded. An second independent observer, who was blinded to the results of the TDI derived data analysis, measured IVA in 40 data sets to assess interobserver variability, and the first observer measured these 40 data sets on a different day to assess intraobserver variability.

Statistical Analysis
Data are expressed as mean ± SD. Measurements of TDI-derived parameters and pressure-volume data at the various stages of preload and afterload modification were analyzed by means of ANOVA for repeated measurements. Linear regression analysis was used to
compare changes in $c_{\text{max}}$ with changes in IVA and isovolumic contraction myocardial velocity. A Bland-Altman analysis was performed on the interobserver data. 14

Results

Influence of Preload and Afterload Changes

During preload reduction, RV end-diastolic volume fell by 34±12% ($P<0.0001$). During afterload increase, RV systolic pressure increased by 54±12% ($P<0.0001$). IVA was unaffected by these changes in preload and afterload, whereas the ejection systolic myocardial velocities (S wave) changed significantly (Table 1 and Figure 2, A and B).

Heart Rate Modulation

There was a positive correlation between IVA and heart rate ($r=0.74$, $P<0.01$). Overall, IVA increased by 135±62% ($P<0.0003$) as heart rate increased from 110 to 190 bpm (Table 2). Simultaneously measured $dP/dt_{\text{max}}$ increased by 76±23% ($P<0.001$). At a heart rate of 210 bpm, however, IVA fell by 5.6±3% and $dP/dt_{\text{max}}$ by 0.3±0.2% from the values measured at a heart rate of 190 bpm (Figure 3), but neither the fall in IVA or $dP/dt_{\text{max}}$ reached statistical significance.

IVA as an Index of RV Contractile Function

During contractility modulation by esmolol infusion, there was no significant fall in $c_{\text{max}}$ of PRSW, but IVA and $dP/dt_{\text{max}}$ fell significantly by 16±19% ($P<0.03$) and 15±13% ($P<0.002$), respectively (Table 3). The other TDI-derived parameters did not change during esmolol infusion.

During dobutamine infusion, we found a significant increase of IVA by 68±73%, $c_{\text{max}}$ by 53±63%, PRSW by 134±84%, and $dP/dt_{\text{max}}$ by 52±19%. Among the other TDI-derived parameters, S-wave velocity increased significantly by 57±29% (Table 3 and Figure 4).

Observer Variability

The mean difference between observer 1 and observer 2 was $8.9±7.6%$. At higher IVA, some differences between observers were outside the confidence limits (Figure 5). The mean intraobserver difference was $5.6±4.3%$.

Discussion

This study demonstrates that IVA measured by TDI reflects RV myocardial contractile function and is unaffected by

<table>
<thead>
<tr>
<th>Cycle Before</th>
<th>Cycle 1 After</th>
<th>Cycle 2 After</th>
<th>Cycle 3 After</th>
<th>Cycle 4 After</th>
<th>Cycle 5 After</th>
<th>P (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Preload reduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVA, m/s$^2$</td>
<td>2.6±1.0</td>
<td>2.5±1.0</td>
<td>2.6±1.0</td>
<td>2.8±1.3</td>
<td>2.8±1.3</td>
<td>2.5±1.3</td>
</tr>
<tr>
<td>IVW, cm/s</td>
<td>7.3±2.9</td>
<td>7.4±2.6</td>
<td>7.6±2.8</td>
<td>7.8±2.9</td>
<td>8.1±3.3</td>
<td>7.6±4.1</td>
</tr>
<tr>
<td>S-wave acc, m/s$^2$</td>
<td>0.8±0.3</td>
<td>0.7±0.2</td>
<td>0.7±0.2</td>
<td>0.7±0.2</td>
<td>0.7±0.2</td>
<td>0.7±0.2</td>
</tr>
<tr>
<td>S-wave velocity, cm/s</td>
<td>6.1±1.6</td>
<td>5.8±1.6</td>
<td>5.2±1.3</td>
<td>5.0±1.5</td>
<td>4.5±1.8</td>
<td>4.3±1.6</td>
</tr>
<tr>
<td>RV end-diastolic volume, m/s</td>
<td>36.7±7.4</td>
<td>33.6±10</td>
<td>31±11</td>
<td>27.2±9</td>
<td>22.9±9.4</td>
<td>19.9±8.2</td>
</tr>
<tr>
<td>$dP/dt_{\text{max}}$, mm Hg/s</td>
<td>306±48</td>
<td>295±54</td>
<td>285±51</td>
<td>275±53</td>
<td>264±50</td>
<td>254±50</td>
</tr>
<tr>
<td>B. Afterload increase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVA, m/s$^2$</td>
<td>2.3±0.6</td>
<td>2.4±0.7</td>
<td>2.3±0.7</td>
<td>2.2±0.7</td>
<td>2.3±0.6</td>
<td>2.2±0.7</td>
</tr>
<tr>
<td>IVW, cm/s</td>
<td>5.5±1.5</td>
<td>5.8±1.3</td>
<td>5.5±1.6</td>
<td>5.2±1.7</td>
<td>4.6±1.4</td>
<td>5.0±1.1</td>
</tr>
<tr>
<td>S-wave acc, m/s$^2$</td>
<td>0.8±0.3</td>
<td>0.7±0.3</td>
<td>0.7±0.3</td>
<td>0.6±0.3</td>
<td>0.6±0.2</td>
<td>0.6±0.2</td>
</tr>
<tr>
<td>S-wave velocity, cm/s</td>
<td>7.1±2.6</td>
<td>6.4±2.9</td>
<td>6.4±2.6</td>
<td>5.7±2.4</td>
<td>5.4±2.0</td>
<td>5.2±1.8</td>
</tr>
<tr>
<td>RV sys pressure, mm Hg</td>
<td>21.6±4.0</td>
<td>24.8±5.4</td>
<td>29.0±4.6</td>
<td>32.1±5.2</td>
<td>32.9±5.3</td>
<td>32.9±5.2</td>
</tr>
<tr>
<td>$dP/dt_{\text{max}}$, mm Hg/s</td>
<td>303±44</td>
<td>340±57</td>
<td>348±68</td>
<td>357±73</td>
<td>353±68</td>
<td>353±67</td>
</tr>
</tbody>
</table>

IVW indicates isovolumic velocity; acc, acceleration; RV, right ventricle; and sys, systolic.
preload and afterload within a physiological range. IVA is also able to detect the force-frequency relation, a phenomenon hitherto unexplored clinically in the intact RV. The myocardial velocity during ejection (S wave) changed in a way similar to IVA during inotropic stimulation but failed to decrease during β-blockade, was affected by changes in preload and afterload, and did not change significantly with heart rate. Although RV function may be abnormal in many patients with acquired and congenital heart disease, pulmonary hypertension and lung disease, and after heart transplantation, all of these diseases may be associated with altered load. The potential advantage of a load-independent index is therefore obvious.

**Indexes of Contractile Function**

Because of its complex geometry, simple M-mode or 2-dimensional echocardiographic indexes cannot reliably be applied for the assessment of RV function. Other noninvasive methods, such as MRI or 3-D echocardiography, can be used accurately to measure end-diastolic and end-systolic volumes and calculate ejection fraction, but these methods are time consuming and, more importantly, these indexes are exquisitely load dependent. This is of particular relevance in congenitally malformed hearts, which are often associated with severe RV pressure or volume overload or a combination of both. We have previously demonstrated that conductance-derived pressure-volume data allow for load-independent measurements of RV contractile function that can be applied accurately and reproducibly in the clinical setting. Conduit catheterization is invasive and time consuming and therefore predominantly used as a research tool for assessment of ventricular function. However, it does provide a gold standard to which other methods of contractility assessment can be compared. A variety of physiological parameters can be derived from the pressure-volume loops. Because the shape of the pressure-volume curve in the RV is different from that of the LV, maximal elastance (e-max) better reflects RV contractile function than does the end-systolic elastance (Ees) commonly used to determine LV contractile function. RV contractile function can also be measured as PRSW. This method yields similar results and is equally reproducible.

**TABLE 2. Myocardial Acceleration and Velocities and dP/dtmax During Different Rates of Atrial Pacing**

<table>
<thead>
<tr>
<th>Heart Rate, bpm</th>
<th>110 (n=6)</th>
<th>130 (n=8)</th>
<th>150 (n=8)</th>
<th>170 (n=8)</th>
<th>190 (n=5)</th>
<th>210 (n=5)</th>
<th>P (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVA, m/s²</td>
<td>2.4±1.2</td>
<td>3.2±1.4</td>
<td>4.2±1.5</td>
<td>4.9±1.3</td>
<td>5.7±1.4</td>
<td>5.4±1.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IVV, cm/s</td>
<td>5.9±2.7</td>
<td>8.0±2.2</td>
<td>9.5±2.6</td>
<td>9.7±3.4</td>
<td>9.0±3.6</td>
<td>9.7±3.8</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>S-wave acceleration, m/s²</td>
<td>0.9±0.3</td>
<td>0.9±0.4</td>
<td>0.9±0.3</td>
<td>1.1±0.4</td>
<td>1.0±0.3</td>
<td>1.1±0.3</td>
<td>&lt;0.07</td>
</tr>
<tr>
<td>S-wave velocity, cm/s</td>
<td>5.4±1.4</td>
<td>6.4±2.1</td>
<td>6.3±1.6</td>
<td>6.6±1.3</td>
<td>6.6±1.9</td>
<td>5.7±1.2</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>dP/dtmax, mm Hg/s</td>
<td>251±41</td>
<td>293±60</td>
<td>319±66</td>
<td>339±70</td>
<td>343±70</td>
<td>342±80</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
In a previous animal experiment with closed-chest pigs, the slope of the end-systolic pressure-volume relation was unaffected by a bolus injection of 1 mg/kg esmolol, whereas dP/dtmax fell significantly. We found a similar phenomenon during a 10-minute infusion of esmolol: emax was unchanged but dP/dtmax fell, a change mirrored by IVA. However, IVA was relatively independent of changes in load, unlike dP/dtmax. These data reinforce the physiological separation between myocardial and cavitary events.

IVA might be considered a surrogate of dP/dtmax because both indexes describe the rate of change of contractile force during isovolumic contraction. We have previously shown that peak IVA precedes the timing of dP/dtmax and has reached a nadir when dP/dtmax is reaching its peak. Indeed, RV dP/dtmax may not even be an isovolumic event in the normal RV. Thus, IVA reflects an earlier isovolumic event and is more robust in terms of load dependency compared with dP/dtmax and more sensitive to changes in contractile state than emax. Furthermore, it is easily measured noninvasively and therefore ideally suited for the assessment of RV contractile function.

**Limitations of the Study**

In this experiment, we measured myocardial acceleration at a fixed position, and thus we cannot evaluate possible regional variations in contractility. The 4-chamber section was chosen because the Doppler interrogation in this view is optimally aligned to the movement of the myocardium from base to apex. This optimal alignment may be more difficult to achieve in the RV than in the LV. Furthermore, the measurement of IVA is not immune to problems of imaging the RV from a transthoracic window, which in some patients may limit the clinical utility of this novel method of contractility assessment. We are unable to comment on the utility of IVA obtained from other views. In the normal LV and RV, myocardial velocities decrease rapidly from base to apex, and IVA may be affected in a similar way. The exact placement of the sample volume becomes a crucial part of studies of contractile function with IVA. The repeated measurements to assess observer variability were made from the prerecorded digital data. Although they included reselection of the site of sample volume placement in the same data set, we did not remove and replace the transducer in a manner in

**TABLE 3. Data at Rest and During Modulation of Contractility by Esmolol and Dobutamine With Simultaneous Assessment of Contractile Function by Conductance Catheterization and TDI**

<table>
<thead>
<tr>
<th></th>
<th>Reduced Contractility</th>
<th>Enhanced Contractility</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Esmol, 1000 μg/kg per minute</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>3.0±0.6</td>
<td>2.5±0.4</td>
</tr>
<tr>
<td>e_max, mm Hg/mL</td>
<td>0.33±0.09</td>
<td>0.31±0.1</td>
</tr>
<tr>
<td>dP/dt_max, mm Hg/s</td>
<td>310±58</td>
<td>255±23</td>
</tr>
<tr>
<td>PRSW</td>
<td>7.2±3.1</td>
<td>4.9±2.3</td>
</tr>
<tr>
<td>IVA, m/s²</td>
<td>3.2±1.7</td>
<td>2.8±1.2</td>
</tr>
<tr>
<td>IVV, cm/s</td>
<td>7.9±3.0</td>
<td>7.6±2.7</td>
</tr>
<tr>
<td>S-wave acceleration, m/s²</td>
<td>0.9±0.2</td>
<td>0.7±0.3</td>
</tr>
<tr>
<td>S-wave velocity, cm/s</td>
<td>6.2±1.9</td>
<td>5.5±1.1</td>
</tr>
</tbody>
</table>

*Figure 3. Measurement of dP/dt_max and IVA during pacing in 8 animals. IVA (right) and dP/dt_max (left) at different rates of pacing are shown.*
which repeated measurements would be made clinically because of time constraints during the experiments. Finally, these data cannot be used to imply utility of this index to detect changes, longitudinally, with progression of disease. Further studies will be needed, but IVA appears to be unique in its ability to monitor acute changes in contractile state and how it may be affected by therapeutic interventions.

Conclusions
IVA is a noninvasive measurement of RV contractile function that is unaffected by of RV loading conditions over a wide range, making it eminently suitable for assessment of patients with acquired and congenital heart disease.

Acknowledgments
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References
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