Relationship Between Early Diastolic Intraventricular Pressure Gradients, an Index of Elastic Recoil, and Improvements in Systolic and Diastolic Function

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Background—Early diastolic intraventricular pressure gradients (IVPGs) have been proposed to relate to left ventricular (LV) elastic recoil and early ventricular “suction.” Animal studies have demonstrated relationships between IVPGs and systolic and diastolic indices during acute ischemia. However, data on the effects of improvements in LV function in humans and the relationship to IVPGs are lacking.

Methods and Results—Eight patients undergoing CABG and/or infarct exclusion surgery had a triple-sensor high-fidelity catheter placed across the mitral valve intraoperatively for simultaneous recording of left atrial (LA), basal LV, and apical LV pressures. Hemodynamic data obtained before bypass were compared with those with similar LA pressures and heart rates obtained after bypass. From each LV waveform, the time constant of LV relaxation ($\tau$), $\pm dP/dt_{\text{max}}$, and $-dP/dt_{\text{max}}$ were determined. Transesophageal echocardiography was used to determine end-diastolic (EDV) and end-systolic (ESV) volumes and ejection fractions (EF). At similar LA pressures and heart rates, IVPG increased after bypass (before bypass $1.64\pm0.79$ mm Hg; after bypass $2.67\pm1.25$ mm Hg; $P<0.01$). Significant improvements were observed in ESV, as well as in apical and basal $+dP/dt_{\text{max}}$, $-dP/dt_{\text{max}}$, and $\tau$ (each $P<0.05$). Overall, IVPGs correlated inversely with both ESV ($\text{IVPG}=-0.027\text{[ESV]}+3.46$, $r=-0.64$) and EDV ($\text{IVPG}=-0.027\text{[EDV]}+4.30$, $r=-0.70$). Improvements in IVPGs correlated with improvements in apical $\tau$ ($\Delta\tau = 5.93\text{[IVPG]}+4.76$, $r=0.91$) and basal $\tau$ ($\Delta\tau = 2.41\text{[IVPG]}+5.13$, $r=-0.67$). Relative changes in IVPGs correlated with changes in ESV ($\Delta\text{ESV} = -0.97\%\text{[IVPG]}+23.34$, $r=-0.79$), EDV ($\Delta\text{EDV} = -1.16\%\text{[IVPG]}+34.92$, $r=-0.84$), and EF ($\Delta\text{EF} = 0.38\%\text{[IVPG]}-8.39$, $r=0.85$).

Conclusions—Improvements in LV function also increase IVPGs. These changes in IVPGs, suggestive of increases in LV suction and elastic recoil, correlate directly with improvements in LV relaxation and ESV. (Circulation. 2001; 104[suppl I]:I-330-I-335.)

Key Words: diastole ■ surgery ■ physiology ■ ventricles

In 1930, Katz\(^1\) speculated that the actively relaxing left ventricle (LV) has the ability to “exert a sucking action to draw blood into its chamber.” Despite these early speculations that diastole was not entirely a passive process, it was not until 1979 that Ling et al\(^2\) demonstrated in a canine model the presence of regional diastolic intraventricular pressure gradients (IVPGs) between the base and apex of the LV. It was speculated that these gradients resulted in the active “sucking” of blood into the LV from the left atrium.\(^2\) Courtois and colleagues subsequently validated these findings in 1988\(^3\) and later demonstrated, also in a canine model, a reduction in IVPG with myocardial ischemia induced by acute coronary occlusion.\(^4\) In this later study, they demonstrated a strong relationship between diastolic IVPG and systolic function, with regional ischemia-induced changes in LV function having a direct effect on IVPG. This observation led them to speculate that IVPGs were related to regional elastic recoil, or the potential energy stored during systole of the LV, and that impairments in regional systolic function would have a significant adverse effect on LV “suction.” Expanding on these concepts, Nikolic and colleagues\(^5\) later confirmed the relationship between IVPG and the elastic restoring forces of the LV in an intermittently nonfilling LV canine model (the mitral valve was intermittently mechanically occluded during diastole). They showed that IVPG was linearly related to the suction volume of the LV, that it was directly influenced by global geometric changes of the LV, particularly in the longitudinal plane, and that it could exist in the absence of LV filling. Nikolic et al\(^6\) had previously demonstrated that volumes below the equilibrium volume (the volume of the...
LV when fully relaxed at zero pressure), which they defined as the suction volume, were directly related to the magnitude of LV elastic recoil, or potential energy, forces. Therefore, these experiments suggested that IVPGs are directly related to LV geometry and are influenced by the regional and global effects of elastic recoil and that overall, they reflect the potential energy stored during systole and represent a mechanism by which the LV can adequately fill under low filling pressures.

Although these animal studies demonstrated that decreases in IVPG correlate with decreases in LV function during acute myocardial ischemia, little is known regarding the potential for increasing these gradients with interventions that improve LV function. Furthermore, although it has been suggested that IVPGs can also exist in humans, data are lacking on the magnitude of these gradients and the influence of perturbations in systolic and diastolic function. Therefore, the goals of the present study, which was conducted in humans undergoing operative interventions aimed at improving LV function through revascularization and/or surgical changes in geometry, were to examine the relationship between different indices of LV systolic and diastolic function on IVPG and the effects of changes in these indices on changes in IVPG.

Methods

Patient Population

After prior approval by our Institutional Review Board was received, written informed consent was obtained from 8 patients (mean age 64.7 ± 8.4 years), of whom 5 were males, before they underwent first-time cardiac surgery requiring cardiopulmonary bypass (CPB). All patients were in sinus rhythm. Operative procedures included isolated CABG in 3 patients, combined CABG and infraorbital exclusion surgery (IES) in 3, isolated IES in 1, and combined CABG and aortic valve repair in 1 patient. Each patient exhibited symptoms and had angiographic evidence of coronary artery disease in which multivessel CABG was the most appropriate indicated therapeutic procedure. In addition, the patients undergoing IES underwent preoperative cardiac MRI to document the extent of myocardial scarring that could be resected. The patient undergoing IES alone had undergone recent percutaneous stent placement and had significant LV dysfunction secondary to an extensive scar in which surgical resection was indicated. Patients undergoing IES were specifically recruited to facilitate evaluation of the effects of significant changes in LV volumes on systolic and diastolic indices under similar loading conditions (ie, left atrial pressures).

Intraoperative Procedure

All patients underwent routine induction of general anesthesia, median sternotomy, and pericardiotomy. After great vessel cannulation and systemic heparinization, a triple-sensor high-fidelity pressure transducer (Millar Instruments) was positioned from a small right superior pulmonary vein stab incision across the mitral valve. The 2 distal pressure sensors were positioned in the LV cavity, while the proximal sensor remained in the left atrium. Before insertion, all catheters were immersed in warm saline for at least 30 minutes to minimize drift, and each individual transducer was calibrated to atmospheric zero. Appropriate anatomic placement was confirmed through the use of transesophageal echocardiography and visualization of appropriate chamber-specific waveforms. Care was taken to ensure that the LV waveforms were not adversely influenced by contact with either the wall of the LV or the mitral valve apparatus.

The signals underwent amplification with a universal amplifier (Gould) and were recorded digitally through an NB-MIO-16 multi-function input/output board (National Instruments) with 12-bit resolution and a sampling frequency of 1000 Hz. The digital signals were recorded with a customized data acquisition and analysis application developed with LabVIEW software (National Instruments) on a standard Pentium-based personal computer running Windows 95.

For each patient, during suspended ventilation, 8-second recordings of intracardiac pressures were obtained before CPB was initiated. To assist in alignment of the pressure waveforms during data recording, the LV was occasionally manually stimulated to allow for an extrasystole that resulted in a prolonged diastolic interval of pressure equalization. This additional step was required to account for the small but nonetheless potentially significant in situ differences in temperature and hydrostatic forces that exist compared with initial ex vivo conditions. After adequate data collection, the catheter was removed and placed in warm saline, myocardial arrest with full CPB support was obtained, and each patient underwent their indicated operative procedure. Myocardial protection was accomplished with conventional Buckberg cardioplegia techniques, which consisted of intermittent combined antegrade and retrograde cardioplegia with vein graft perfusion as needed. Coronary revascularization was performed by standard techniques, including the use of internal mammary and radial artery grafts when available. IES was performed based on techniques described previously. Each patient was successfully and completely weaned from CPB with intermittent volume infusions from the CPB circuit to obtain adequate hemodynamics by increasing preload. At this time, after rezeroing, the catheter was repositioned across the mitral valve, and multiple hemodynamic measurements were obtained in 8-second intervals during different stages of physiological stabilization to allow for matching of the hemodynamic data with pre-bypass values. During this period of data collection, no patient required vasopressor, inotropic, or external pacing support. After data collection, the catheter was removed, systemic heparinization was reversed, and the operative procedure was concluded in the conventional fashion. All patients tolerated this protocol well and without complications.

Data Analysis

Clinical Data

For each 8-second physiological condition measured, 3 representative complete-cycle waveforms were analyzed with a customized LabVIEW data analysis application. The mean of these 3 values was then used for pre-bypass versus post-bypass statistical comparison. From the left atrial pressure waveforms, the mean left atrial pressure was determined. From the 2 LV pressure waveforms (apex and base), the maximum positive and negative rates of pressure change (\(\frac{dP}{dt}\) max , respectively) were determined, as was the time constant of isovolumic relaxation (\(r\)). The \(r\) was determined with Weiss’ monoeponential equation from each LV pressure waveform after curve fitting by use of the Levenberg-Marquardt nonlinear least-squares parameter estimation technique. As validated by Yellin et al., a zero asymptote (b=0) was used. The same customized analysis software was used to determine peak and mean early diastolic LVbasal-LVapical gradients (IVPGs; Figure 1).

In addition, heart rate and systemic blood pressure (systolic, diastolic, and mean), measured from a radial arterial line, were also recorded. Transesophageal echocardiography with conventional, commercially available ultrasound equipment was also used before and after CPB to determine LV end-diastolic and end-systolic volumes (EDV and ESV, respectively) by Simpson’s biplane disc method from digitally stored images. Stroke volume (SV) and ejection fraction (EF) were also determined. All echocardiographic and hemodynamic measurements were obtained simultaneously with the intracardiac pressure measurements to allow for synchronization of all variables.

Statistical Analysis

All statistical analysis was performed with Systat 9.0 (SPSS Inc). Paired Student’s t tests were used to compare pre- and post-CPB results. Linear regression analysis was performed to determine the relationship between IVPG and the echocardiographic volumes and hemodynamic indices. Similarly, regression analysis was also per-
Results
LV Systolic and Diastolic Function Before and After Surgery
Left atrial pressures, heart rates, and SVs before and after operative intervention (all P=NS; Table) were similar overall. However, there were significant improvements in ejection fraction and ESV (both P<0.05; Table). Although EDV decreased after patients were weaned from CPB (pre-bypass 79.7±38.7 versus post-bypass 66.9±22.6 mL), this change was not statistically significant overall (P=0.13) except in the 4 patients undergoing IES, in whom EDV decreased from 111.9±38.1 to 76.5±30.4 mL (P=0.03). In the other 4 patients, EDV increased insignificantly from 55.6±15.0 to 59.7±15.6 mL (P=0.36). In addition, from the pressure transducers, LV basal +dP/dt max improved from 890±101 mm Hg/s (range 761 to 1075 mm Hg/s) to 1128±220 mm Hg/s (range 826 to 1426 mm Hg/s, P<0.01 versus pre-bypass); similarly, LV apical +dP/dt max improved from 909±114 mm Hg/s (range 758 to 1100 mm Hg/s) to 1094±221 mm Hg/s (range 788 to 1455 mm Hg/s, P<0.01 versus pre-bypass).

Similar to the improvements in systolic function, diastolic function also improved after operative intervention. Apical −dP/dt max and τ both improved after intervention (−830±207 to −984±267 mm Hg/s and 62.5±12.2 to 51.6±8.3 ms, both P<0.05 pre-bypass versus post-bypass), as did basal −dP/dt max and τ (−857±199 to −971±255 mm Hg/s and 55.2±13.4 to 47.6±12.0 ms, both P<0.05 pre-bypass versus post-bypass).

LV IVPGs Before and After Intervention
In all cases, peak IVPG was positive and occurred toward the end of relaxation, during which LV pressures were at their minimum. Peak IVPG before CPB was 1.64±0.79 mm Hg (range 0.50 to 2.80 mm Hg) and increased to 2.67±1.25 mm Hg (range 1.20 to 5.14 mm Hg) after patients were weaned from CPB (P<0.01). Similarly, mean IVPG increased from 0.92±0.64 to 1.51±0.74 mm Hg (P<0.01). Overall, all patients increased their peak IVPG by 1.03±0.75 mm Hg (37.9±20.8%).

Overall, pre-bypass and post-bypass IVPG correlated inversely with both EDV (IVPG=−0.027[EDV]+4.30, r=−0.70, P<0.001; Figure 2, top) and ESV (IVPG=−0.027[ESV]+3.46, r=−0.64, P<0.001; Figure 2, bottom). In addition, similar inverse correlations were observed between mean IVPG and EDV (r=−0.62) and ESV (r=−0.54). A linear relationship was observed between IVPG and both apical and basal +dP/dt max (r=0.54 and r=0.57, respectively, both P<0.01). Although no correlation was observed between IVPG and apical or basal τ or −dP/dt max, or the apical to basal differences in these values, improvements in IVPG correlated with improvements (ie, shortening) in apical τ (Δτ=5.93[ΔIVPG]+4.76, r=0.91, P<0.001; Figure 3) and, to a lesser extent, basal τ (Δτ=2.41[ΔIVPG]+5.13, r=0.67, P<0.001; Figure 3). In addition, improvements in the percent increase in IVPG correlated linearly with volume indices of LV systolic function, namely, ESV (ΔESV=−0.97[ΔIVPG]+23.34, r=−0.79, P<0.001; Figure 4), EDV (ΔEDV=−1.16[ΔIVPG]+34.92, r=−0.84, P<0.001; Figure 4), and EF (ΔEF=0.38[ΔIVPG]−8.39, r=0.85, P<0.05; Figure 5).

Discussion
Our findings confirm the existence of a quantifiable IVPG during early diastolic filling in humans. Furthermore, we demonstrate that improvements in LV systolic and diastolic
function, through operative myocardial revascularization and/or LV remodeling, result in increases in these gradients. These findings complement previous animal experiments that demonstrated reductions in IVPG secondary to acute ischemia and impairments in LV systolic function.

Early work investigating the determinants of IVPG by Courtois et al\(^4\) demonstrated significant decreases in IVPG with acute coronary occlusion from 1.2±0.5 to 0.6±0.6 mm Hg, changes that are consistent with our in situ observations. In addition, they demonstrated a relationship between decreases in IVPG and extensive regional systolic dysfunction. These findings, in conjunction with their previous work,\(^3\) contributed to their speculation of the relationship between IVPG and the elastic recoil of the LV and provide a mechanism to maintain LV filling at lower diastolic pressure. Through impairments in regional systolic function, less energy would be released during diastole, which in turn would result in decreased or abnormal intraventricular flow. These observations are consistent with our findings of not only a relationship between IVPG and ESV but also of a relationship between the change in IVPG and changes in ESV, thereby validating the hypothesis relating the elastic recoil of the LV to IVPG. Furthermore, the lack of a relationship between IVPG and left atrial pressures (\(y = -0.052x + 2.47, r = 0.27, P > 0.05\)) combined with the observations by Nikolic et al in their nonfilling LV model\(^5\) suggest that although these early gradients may exist in the absence of LV filling, they may represent intrinsic properties of the LV and transmitral pressure gradients.

To elaborate on the relationship between diastolic filling and IVPG, Steine and colleagues\(^11\) compared results of color M-mode echocardiography, a technique that allows for noninvasive visual estimation of LV filling patterns, with invasively obtained pressure gradients. In their canine model of LV dysfunction, using coronary microembolization, IVPG decreased from 1.9±0.9 to 0.7±0.5 mm Hg. In addition to also observing an inverse relationship to ESV (\(r = 0.95, P < 0.01\)), they demonstrated that IVPG was inversely related

### Table: Physiological Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before CPB</th>
<th>After CPB</th>
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</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>62–114</td>
<td>67–87</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>77.0–121.0</td>
<td>95.0±141.0</td>
</tr>
<tr>
<td>Diastolic</td>
<td>47–73</td>
<td>51–77</td>
</tr>
<tr>
<td>Mean</td>
<td>58–89</td>
<td>61–84</td>
</tr>
<tr>
<td>EDV, mL</td>
<td>38.4–145.3</td>
<td>37.1–95.0</td>
</tr>
<tr>
<td>ESV, mL</td>
<td>17.7–111.8</td>
<td>16.7–57.7</td>
</tr>
<tr>
<td>SV, mL</td>
<td>14.6–38.9</td>
<td>17.1–40.5</td>
</tr>
<tr>
<td>EF, %</td>
<td>21–65</td>
<td>38–62</td>
</tr>
<tr>
<td>Mean LA, mm Hg</td>
<td>6.74–19.86</td>
<td>7.87–23.23</td>
</tr>
<tr>
<td>Mean LA pressure, mm Hg</td>
<td></td>
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LA indicates left atrial.

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**Figure 2.** Relationship between IVPG and EDV (top) and ESV (bottom). Each line represents changes for individual patient, with solid circles representing preintervention values and open circles representing postintervention results. Thick solid lines are averages for all data points. Stars indicate patients who underwent IES.

**Figure 3.** Relationships between absolute changes in IVPG and in apical (solid circles) and basal (open circles) \(r\).
myocardial protection strategies, post-CPB LV dysfunction is less common and is illustrated by the lack of inotropes or vasopressors needed on weaning patients in the present study from CPB. In addition, IES, a technique in which the LV is surgically remodeled by resecting apical tissue scarred by myocardial infarction, has also recently been shown both by our group and others to result in significant improvements in LV systolic and diastolic function.17–19 Inclusion of these patients was done to illustrate that improvements in IVPG can also occur with iatrogenic changes in ventricular geometry. Although the independent effects of IES cannot be separated from the effects of revascularization, the inclusion of these different operative modalities clearly illustrates the increases in ventricular suction that coincide with improvements in both systolic and diastolic function.

Study Limitations
There are several significant limitations to our human study. Although we suggest that improvements in IVPG coincide with improvements in elastic recoil through an inverse relationship with ESV, we did not actually measure either the elastic recoil of the LV or the suction volume. The suction volume is defined as the difference between the smallest measured LV volume and LV volume at zero pressure, a property that may be technically difficult to determine precisely in humans. In addition, although it has been suggested that IVPGs reflect the elastic recoil and release of potential energy, it is yet to be demonstrated whether this process is secondary to a passive release of stored energy or whether this “suction” is an active energy-consuming component of early diastole. Another limitation is our intraoperative model. Although the effects of an intact pericardium are known to affect diastolic filling20 and alter end-diastolic LV pressure-volume relationships,21 the timing of these influences during diastole is such that they should have little influence on early-diastolic physiology. In addition, despite the limited number of patients studied and the different operative procedures performed, our results nonetheless validate the physiological relationships observed.

Potential Clinical Applications
Recent advances in color Doppler echocardiography may allow for noninvasive measurements of IVPG. By abstraction of the spatiotemporal velocity characteristics of color M-mode echocardiography, a pressure gradient along an imaging scan line, such as mitral inflow, can be derived.22 These techniques have been shown to accurately measure transmural pressure gradients in a canine model23 and more recently in humans.24 The ability to directly and noninvasively quantify this index of LV function may allow for better assessment of cardiac function in response to various interventions, such as pharmacological echocardiographic stress testing or intraoperative assessment of surgical interventions, or as a component of serial examinations of functional status.

Conclusions
IVPGs, a previously demonstrated index of LV elastic recoil and early diastolic suction, increase with operative interventions that improve both systolic and diastolic function.
Furthermore, changes in these gradients are directly related to improvements in ESV, an index of LV contractility, and, an index of LV relaxation.

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References
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