Pacing-Induced Dilated Cardiomyopathy Increases Left-to-Right Ventricular Systolic Interaction

David J. Farrar, PhD; John C. Woodard, PhD; Edna Chow, PhD

Background. The right ventricle (RV) receives part of its systolic pumping force from the left ventricle through systolic ventricular interaction. The purpose of this study was to determine the effects of dilated cardiomyopathy on left ventricular to right ventricular (LV-to-RV) systolic interaction.

Methods and Results. Studies were performed in six normal pigs and in six pigs in which dilated cardiomyopathy resulting in congestive heart failure (CHF) was produced with rapid ventricular pacing at 230 beats per minute for 1 week. In all pigs, we rapidly withdrew blood from the LV apex into a prosthetic ventricle in a single beat, which reduced LV systolic pressure without changing RV or LV end-diastolic pressure, and the resultant instantaneous changes in RV systolic pressure and pulmonary artery flow were determined. The LV-to-RV mean systolic interaction gain was calculated as the change from a normal beat to the instantaneous unloaded beat in mean RV systolic pressure divided by the change in mean LV systolic pressure. Mean systolic pressure gain was approximately 2.5 times greater (P < .05) in the CHF animals (0.103 ± 0.018 mm Hg/mm Hg) than in the normal pigs (0.040 ± 0.011 mm Hg/mm Hg).

Conclusions. These data demonstrate that left-to-right ventricular systolic interaction is significantly greater in dilated cardiomyopathy compared with the normal heart, indicating that the contribution of the left ventricle to RV systolic pressure generation has increased. This is consistent with decreased elastance of the interventricular septum resulting in increased coupling between the ventricles. (Circulation 1993;88:720-725)

KEY WORDS • ventricular interdependence • septal compliance

Ventricular interactions during systole and diastole are important determinants of ventricular function. Various terms have been used to describe these phenomena, including ventricular interference, cross talk, interdependence, and ventricular interaction. Diastolic ventricular interaction is due to the volume of one ventricle impinging on the volume of the contralateral ventricle. On the other hand, systolic ventricular interaction, rather than impairing the contralateral ventricle, is responsible for transmission of systolic forces from one ventricle to the other, resulting in an increase in the "effective contractility" of the contralateral ventricle over and above its native contractility. This is especially important for the low-pressure right ventricle, which is assisted during ejection by forces from the left ventricle transmitted mainly through the interventricular septum and the common muscle fibers of the free walls.

The role of systolic interaction in various forms of heart disease has not been fully studied. Little et al. in studies of right ventricular (RV) pressure-overload hypertrophy, and Slinker et al. in studies of left ventricular (LV) pressure-overload hypertrophy, have found that RV-to-LV ventricular interaction decreases during hypertrophy, which is attributed to a stiffening of the interventricular septum. We hypothesize that the opposite occurs during dilated cardiomyopathy, that ventricular interaction increases and becomes an increasingly important determinant of cardiac function, especially for the right ventricle. We test this hypothesis by comparing LV-to-RV isolated systolic ventricular interaction gains in the normal intact porcine heart with gains measured in a pacing-induced dilated heart failure model.

Methods

Surgical and instrumentation protocols have been described previously for the pacing-induced model of dilated heart failure and for determining isolated systolic ventricular interaction gains. The present study consists of ventricular interaction measurements obtained in 12 new experimental pigs divided equally into two groups: a normal group and congestive heart failure (CHF) group. The six normal pigs (average body weight, 41.6 ± 2.1 kg) proceeded directly to the instrumentation and data collection protocols. The six CHF pigs (weight, 44.2 ± 1.7 kg) underwent rapid ventricular pacing for 1 week before data collection. These protocols are briefly reviewed here.
Model of Congestive Heart Failure

After anesthesia with ketamine (20 mg/kg IM for preinduction) and intravenous injections of thiamylal sodium (4.5 mg/kg initial bolus and 2.5 mg/kg maintenance doses every 15 to 20 minutes), the six pigs from this group were intubated and connected to an artificial ventilator. Respiratory rate, tidal volume, and FIO2 were adjusted as necessary to maintain acid-base equilibrium. A Medtronic unipolar sutureless pacemaker lead was attached to the LV apex through a small opening in the diaphragm under the xiphoid process and connected to a Medtronic pacemaker (modified model SX-5985) implanted in a subcutaneous abdominal pocket. After recovery from anesthesia, the pigs were returned to a chronic care facility, where they received a standard diet, free access to water, and an antibiotic regimen of penicillin-G. The pacemaker was then programmed at a rate of 230 beats per minute. Seven days later, the animals were brought back to the laboratory for the acute experiment. Before induction of general anesthesia, the pacemaker was turned off. The chest was opened, and the heart was instrumented as described below.

Instrumentation

In the six CHF pigs and the six normal pigs, the heart was exposed through a median sternotomy and implanted with a modified Thoratec (Berkeley, Calif) ventricular assist device (VAD), which is a sac-type prosthetic ventricle (Fig 1). The VAD was modified by removal of the usual mechanical inflow and outflow valves, and the outflow port was blocked off. A 12-mm id wire-wrapped cannula was inserted into the LV apex via a stab incision, and the cannula was connected to the VAD inflow port. The VAD pneumatic control console was also modified to create single-cycle operation, in which there is rapid filling of the VAD and therefore rapid unloading of the left ventricle upon command in a single beat immediately after the R wave of the ECG. Left and right ventricular pressures (LVP, RVP) were measured with high-fidelity Millar microtip catheters (Millar Instruments, Inc, Houston, Tex). These transducers were zeroed in blood at body temperature before insertion and checked at the end of the experiment. Aortic pressure (AoP) was measured with a standard fluid-filled catheter positioned in the carotid artery and was connected to a pressure transducer (Statham, Oxnard, Calif). An electromagnetic flow probe (Carolina Medical Electronics, Inc, King, NC) was placed around the pulmonary artery to measure continuous beat-to-beat cardiac output (CO). All signals were continuously recorded on an eight-channel Gould chart recorder and simultaneously sampled on line at 100 samples per second with a Metabyte analog-to-digital converter (Taunton, Mass) connected to a personal computer.

Experimental Protocol

All data were collected after a stabilization period of 15 to 30 minutes subsequent to completion of instrumentation and VAD implantation. The basic protocol consisted of measurements in data groups that were 8 seconds in duration, with the respiration held at end expiration. In each group, there were six normal cardiac cycles followed by one experimental beat with rapid left ventricular unloading. Unloading was achieved after the R wave of the seventh beat by rapidly reducing the pneumatic pressure of the VAD from 200 to -100 mm Hg, thus allowing the VAD to fill directly from the left ventricle. The instantaneous changes produced by this perturbation on the right ventricle were then evaluated.

Data Analysis

Data were analyzed using a data acquisition and analysis software package developed in our laboratory. Data sets with evidence of arrhythmias or cycle-to-cycle instability were discarded. Mean systolic pressures were calculated by integration of LVP and RVP during systole. Two measurements of systolic LV-to-RV interaction gains were determined: (1) mean ventricular systolic pressure gain and (2) instantaneous systolic gain. Mean ventricular pressure gain (mm Hg/mm Hg) was defined as the ratio of changes in mean RV systolic pressure divided by changes in mean LV systolic pressure for each of the six normal beats compared with the unloaded beat. The instantaneous LV-to-RV pressure gain at a given time (t) during systole was defined as the ratio of the change in RVP to the change in LVP from the control to the unloaded beat at time t. The systolic period was normalized such that the time from end diastole to end ejection ranged from 0.0 to 1.0. This period was divided into 21 pressure points in 5% increments of normalized systolic time. The pressure values at these normalized times were determined by linear interpolation of the sampled points. The instan-
Table 1. Changes in Ventricular Pressures and Right Ventricular Function Before and During the Unloaded Beat

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Control beat</th>
<th>Unloaded beat</th>
<th>Percent change</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV Volumetric Stroke Work</td>
<td>Normal</td>
<td>75.8±11.2</td>
<td>30.0±6.8</td>
<td>-60.3±7.7§</td>
</tr>
<tr>
<td>(mm Hg) CHF</td>
<td>63.7±10.9</td>
<td>22.5±8.9</td>
<td>-64.5±11.3§</td>
<td></td>
</tr>
<tr>
<td>RV Volumetric Stroke Work</td>
<td>Normal</td>
<td>19.7±4.3</td>
<td>38.5±4.0</td>
<td>-9.7±4.0§</td>
</tr>
<tr>
<td>(mm Hg) CHF</td>
<td>26.3±6.7</td>
<td>22.1±6.6</td>
<td>-16.6±5.3§</td>
<td></td>
</tr>
<tr>
<td>LV End-diastolic Pressure</td>
<td>Normal</td>
<td>10.4±4.0</td>
<td>10.6±4.0</td>
<td>2.9±2.3</td>
</tr>
<tr>
<td>(mm Hg) CHF</td>
<td>17.0±10.0</td>
<td>14.8±7.2</td>
<td>-8.7±12.6</td>
<td></td>
</tr>
<tr>
<td>RV End-diastolic Pressure</td>
<td>Normal</td>
<td>3.2±2.0</td>
<td>3.8±1.9</td>
<td>-2.5±4.2</td>
</tr>
<tr>
<td>(mm Hg) CHF</td>
<td>7.3±2.6</td>
<td>7.1±2.5</td>
<td>-1.7±1.8</td>
<td></td>
</tr>
<tr>
<td>CO</td>
<td>Normal</td>
<td>3.8±1.1</td>
<td>3.7±1.4</td>
<td>-2.3±18.2</td>
</tr>
<tr>
<td>(L/min) CHF</td>
<td>2.2±0.7</td>
<td>1.5±0.6</td>
<td>-28.5±24.8§</td>
<td></td>
</tr>
<tr>
<td>RVSV</td>
<td>Normal</td>
<td>35.5±7.6</td>
<td>29.4±8.9</td>
<td>-18.4±12.6§</td>
</tr>
<tr>
<td>(mL) CHF</td>
<td>21.9±7.6</td>
<td>13.9±5.4</td>
<td>-36.5±16.1§</td>
<td></td>
</tr>
<tr>
<td>RVSW</td>
<td>Normal</td>
<td>0.121±0.044</td>
<td>0.092±0.041</td>
<td>-26.5±13.1§</td>
</tr>
<tr>
<td>(J) CHF</td>
<td>0.073±0.032*</td>
<td>0.039±0.021*</td>
<td>-46.7±15.2§</td>
<td></td>
</tr>
<tr>
<td>T90 (s)</td>
<td>Normal</td>
<td>0.283±0.032</td>
<td>0.268±0.042</td>
<td>-5.7±6.3</td>
</tr>
<tr>
<td>CHF</td>
<td>0.277±0.073</td>
<td>0.233±0.073</td>
<td>-16.5±7.4§</td>
<td></td>
</tr>
</tbody>
</table>

LV, left ventricular; RV, right ventricular; MSP, mean systolic pressure; EDP, end-diastolic pressures; CO, cardiac output; SV, stroke volume; SW, stroke work; T90, duration of pulmonary artery ejection; CHF, congestive heart failure. *P < .05, †P < .01 (CHF compared with normal); ‡P < .05, §P < .01 (unloaded beat compared with control beat).

In 25% of the pool, there were instantaneous gains were determined for the last 70% of systole, by which time there was a consistent reduction in LVP during unloading.

RV stroke volume was computed by integration of pulmonary artery flow for the whole cardiac cycle, and RV stroke work was computed by the product of RV pressure times stroke volume. Zero-flow baseline was established as the average signal in the last 25% of the cycle before the beginning of systole. In each group, the data from the control cycles (ie, not unloaded) were averaged to provide one value for each parameter. Data sets were repeated 5 to 10 times for each experiment and subsequently averaged for each animal. Next, the data from all animals in each group were pooled. All results shown are mean ± 1 SD. Statistical comparisons between normal and CHF pigs were performed with a nonpaired t test and between control and unloaded beats with a paired t test. Statistical significance of changes in instantaneous gains was determined by a two-way ANOVA (CHF versus normal and time) with repeated measures on one factor (time). A P value of < .05 was considered significant.

All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH Publication No 80-23, revised 1978).

Results

Pigs with CHF had depressed CO, stroke volume, and stroke work and elevated RV end-diastolic pressures compared with the normal pigs (Table 1). Although the CHF animals had elevated heart rates during pacing, there was no difference in resting heart rate between CHF pigs (105±10 beats per minute) compared with normal pigs (102±21 beats per minute) during the experimental measurements.

Data showing the effects of LV unloading on RV pressure and pulmonary artery (PA) flow from a typical normal pig and a pig with CHF are shown in Fig 2. Pressure and flow waveforms from the acutely unloaded beats are shown superimposed on the corresponding control cardiac cycle in dashed lines.

FIG 2. Waveforms: Instantaneous effects of reducing left ventricular pressure (LVP) on right ventricular pressure (RVP) and pulmonary artery (PA) flow are shown as typical examples from one normal pig (left) and one pig in pacing-induced congestive heart failure (CHF, right). Data measured in a single unloaded beat are shown superimposed on the preceding (control) cardiac cycle in dashed lines.
function of mean gains (mm Hg) compared to right systolic instantaneous gains of CHF, maximum 0.095±0.038 0.027±0.026 0.088±0.029

CHF, congestive heart failure. t = normalized time during systole. *P < .05; †P < .01; ‡P = .24.

ventricular interaction can be quantitated by interaction "gains," which are ratios of changes in pressure in one ventricle produced by changes in the other ventricle. Absolute values of interaction gains have been shown to be substantially less during systole than diastole but important for both. For example, Slinker et al26 have measured diastolic interaction gains of 0.33 from the right ventricle to the left ventricle, meaning that for every 1 mm Hg change in end-diastolic pressure in the right ventricle, there was a corresponding change in end-diastolic pressure of 0.33 mm Hg in the left ventricle. In contrast, systolic pressure gains have been reported for LV-to-RV interaction to range in different experimental preparations from 0.040 mm Hg/mm Hg in intact dog hearts,34 0.054 mm Hg/mm Hg in the intact porcine heart,35 0.08 in an isolated canine heart,22 and 0.086 calculated from data during a sudden increase in aortic afterload in intact dog heart.9 Although an LV-to-RV systolic pressure gain of 0.05 to 0.10 appears small, it is actually a significant determinant of RV systolic function.34,35 With an LV systolic pressure of 100 mm Hg, this would correspond to a sizeable contribution of 5 to 10 mm Hg to RV systolic pressure, which is 20% to 40% of RV peak systolic pressure34,35 and up to 43% of RV stroke work.35 Maughan et al24 and Yamaguchi et al34 have demonstrated that the RV-to-LV systolic gain is actually greater than from LV-to-RV, but the corresponding absolute magnitude of the contribution to LV pressure is quite small. Therefore, the significance of systolic ventricular interaction is greater for the right ventricle than for the left ventricle.34

We recently presented our experimental method of determining isolated systolic pressure interaction gain in the intact heart using the same techniques as in the present study.35 The rapid removal of blood from the left ventricle after the R wave in a single systole assures that end-diastolic conditions are unaltered and that the resultant changes in RVP are due solely to isolated systolic interactions. In the current series of normal hearts, the mean systolic pressure gains averaged 0.040±0.011, identical to that of Yamaguchi et al24 and not significantly different from the gain of 0.054±0.017 in our previous report.35 Furthermore, the current study shows that the pacing-induced model of dilated CHF increases the mean systolic pressure gain almost 2½ times that of the normal pigs, to 0.103±0.018 mm Hg/mm Hg. The experimental reduction in mean systolic LVP produced during rapid unloading was the same in both groups of animals. However, the resultant change in mean systolic RV pressure was significantly greater in the CHF
pigs than in the normal pigs, thus yielding the elevated calculation of gain. We have shown previously that rapid ventricular pacing in this model results in biventricular dilation with no change in wall thickness and is a realistic model of dilated cardiomyopathy. Thus, we can deduce that the contribution of the left ventricle to RV pressure increase significantly in dilated cardiomyopathy.

The instantaneous systolic gains are also significantly increased in the CHF animals compared with normal animals throughout the latter part of systole. These data confirm our previous findings that systolic interaction gains are time varying within systole. This may explain some of the variability of measurements between researchers that used different techniques and made measurements at different times within the cycle. The data also show that the pattern of time-varying interaction gain is markedly different for CHF animals compared with normal animals. However, there are some limitations to these methods that should be noted. First, the experiment was designed to determine the response throughout systole to LV unloading starting early in the beat. The different responses in late systole between CHF and normal animals could be due partially to RVP changes not being made at the same RV volumes. A different response may have resulted if single measurements were made after unloading at different times during systole. Also, the fact that LV unloading reduces the duration of PA ejection in the CHF animals also would have some effect on the calculation of gains at normalized systolic times.

It is well known that the principal cause of right heart failure is left heart failure. Two known mechanisms related to ventricular interaction are responsible for depressed RV function during LV failure: pulmonary hypertension and diastolic ventricular interaction. Pulmonary hypertension can occur when poor LV systolic function results in increased left atrial pressure, increased pulmonary venous pressures, and a decrease in PA pressure and RV afterload (initially via indirect hemodynamic interactions). Diastolic ventricular interactions can have a negative effect on RV function during LV failure when the left ventricle dilates and the septum shifts to the right, reducing diastolic RV compliance and impairs RV filling. Less is known about the role of systolic ventricular interactions in heart failure, but the results in the current study suggest that systolic interactions become increasingly important and may help the right ventricle compensate for any loss in native contractility. However, during severe left heart failure with reduced LV pressure, there would be a corresponding reduction in the LV contribution to systolic pressure generation of the right ventricle.

The results of the present experiment are also directly relevant to right heart failure in heart failure patients who are supported with left VADs (LVADs). LVP can be reduced significantly during normal operation of the LVAD, which could thereby reduce the contribution of LVP to RV via systolic ventricular interaction. The results from the present study provide an explanation for the finding that there is no significant change in RV function during LV unloading with an LVAD in normal hearts, whereas significant impairment of RV function has been reported during LV unloading in pigs with pacing-induced CHF. The explanation is that with increased systolic ventricular interaction in the CHF pigs, the reduction in LVP resulted in a much greater loss of LV systolic contribution to RVP generation than in the normal heart. The relative importance of ventricular interaction in LVAD patients is unknown but will probably be quite variable and could be more than offset by other factors such as the reversal of passive pulmonary hypertension and reduced right-heart afterload.

Santamore and Burkoff have developed a mathematical model of the effects of ventricular interaction on the circulatory system. They incorporated the three-compartment model of Maughan et al., which describes systolic ventricular interaction as consisting of three elastances representing the RV free wall, the interventricular septum, and the LV free wall. In this model, the pressure in the right ventricle is a function of native Emax contractility and volume plus the systolic interaction gain times the LVP. Thus, they concluded that the “effective” contractility of the right ventricle can be greater than the native Emax contractility because of the presence of systolic interaction. LV-to-RV systolic ventricular interaction gain (G) in their model is determined to be the parallel combination of the elastances of the RV free wall (Erv) and the interventricular septum (Ei):

\[ G = E_{rv}/(E_{rv} + E_{i}) \]

If the interventricular septum is very stiff compared with the RV free wall, then G approaches zero, and there is no systolic interaction between the ventricles, whereas if the septum is very compliant (such as a thin rubber membrane), then ventricular interactions are much larger, with G approaching one. If we use this model to describe the 2½-fold increase in systolic gain during CHF observed in the present study, then we can conclude that septal elastance has decreased significantly more than the RV free wall during CHF. In the normal heart, a gain of 0.04 would indicate that Ei is 24 times greater than Erv; in the CHF pigs, a gain of 0.10 would indicate that there has been a relative reduction in Ei to only nine times greater than Erv. This conclusion is consistent with the findings by Little et al. and Slinker et al., who observed decreased ventricular interaction during chronic pressure-overload hypertrophy, which was attributed to decreased septal compliance. Thus, systolic interaction is decreased during conditions in which the septum is less compliant, such as hypertrophy, and is increased during conditions in which the septum is more compliant, such as dilated cardiomyopathy.

Acknowledgments

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