Left-to-right systolic ventricular interaction in patients undergoing biventricular stimulation for dilated cardiomyopathy

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Osculati G, Malfatto G, Chianca R, Perego GB. Left-to-right systolic ventricular interaction in patients undergoing biventricular stimulation for dilated cardiomyopathy. J Appl Physiol 109: 418–423, 2010. First published May 20, 2010; doi:10.1152/japplphysiol.00770.2009.—Left-to-right systolic ventricular interaction (i.e., the phenomenon by which the left ventricle contributes to most of the flow and to two-thirds of the pressure generated by the right ventricle) originates from transmission of systolic forces between the ventricles through the interventricular septum and from the mechanical effect of the common muscle fibers encircling their free walls. As a consequence, any reduction of left ventricular free wall function translates in lower right ventricular pressure or function. We investigated whether systolic ventricular interaction could be evidenced in nine patients with dilated cardiomyopathy in whom a biventricular pacemaker was implanted. Changes in right and left ventricular pressures were measured with high-fidelity catheters, before and after periods of biventricular pacing from the right atrium with different stimulation intervals to the right and left ventricles, respectively. The steady-state changes of left and right ventricular systolic pressure obtained from any single pacing interval combination were considered. We then calculated, with a two-level mixed regression analysis of the entire data set, the relation between changes in left and right systolic pressures: the presence of a statistically significant slope was assumed as evidence of ventricular interaction. The slope of the regression replaced the crude pressure ratio as an estimate of the gain of the interaction; its value compared with values observed in experimental studies. Moreover, its dependence on septal elastance and on right ventricular volume was similar to that already demonstrated for ventricular interaction gain. In conclusion, the linear relationship we found between systolic pressure changes in the two ventricles of patients with dilated cardiomyopathy during biventricular pacing could be explained in terms of ventricular interaction.

METHODS

Nine patients (71 ± 7 yr, range 59–81 yr; 7 men, 2 women), in whom definitive biventricular pacing was clinically indicated because of advanced dilated cardiomyopathy, left bundle branch block (LBBB), and QRS > 150 ms, were acutely studied during the implant procedure; one patient was in atrial fibrillation. All patients gave their written informed consent to the study, which conformed to the principles outlined in the Declaration of Helsinki and had previously been approved by the Ethical Committee at our institution.

Study protocol. Three stimulation catheters, subsequently used for definitive implant, were placed in the right atrium at the RV apex, and in a lateral or posterolateral cardiac vein, respectively, for right atrium, RV, and LV stimulation. Catheters were connected to two external stimulators, in order to allow changes in the stimulating intervals between the right atrium and each of the two ventricles independently. Two high-fidelity Millar microtip catheters (Millar Instruments, Houston, TX) connected to the appropriate carrier amplifier (DA 100C Biopac Systems, Goleta, CA) and calibrated according to the manufacturer’s instructions, were positioned in each ventricle. The analog signal from the carrier amplifiers was sampled at 200 Hz and stored on a personal computer with a commercially available system (Biopac 150 System): 30 s of RV and LV pressure...
was recorded $J$ in control conditions, i.e., without any stimulation (if permitted by the spontaneous heart rate) or during atrial stimulation in AAI mode and 2) with biventricular stimulation both in VAT mode and in DDD mode, the last at a frequency 10% above the spontaneous rhythm in order to have an uninterrupted ventricular stimulation. The pacing intervals to the RV (A-RV) and to the LV (A-LV) were separately and independently changed in 20-ms steps in a range from 60 to 160 ms according to a randomly applied grid in which any possible combination was contemplated (the atrial fibrillation patient received VVI-mode stimulation with different intervals between the 2 ventricle stimulations). This allowed a series of ventricular pressure measurements for each patient, from which a data set of 369 measures was built.

Data analysis. All data were analyzed off-line with Biopac System software. From each ventricular pressure curve, the maximum change in pressure over time (dP/dt) (dP/dtmax) was obtained by a 5-point weighted slope. Systolic pressure was measured at its maximum value, while end-diastolic pressure was measured at the value corresponding to 10% of the dP/dtmax (12, 14). Mean values of each variable were obtained by averaging all 30-s records for every pair of stimulation intervals changes with respect to control were calculated as the difference ($\Delta$) between the actual and the basal mean values.

Left-to-right systolic interaction analysis. For the entire population, data obtained during all stimulation protocols in all patients were pooled in order to obtain a single data set. Interventricular interaction was derived from a mixed regression analysis (as detailed in Statistical analysis below) between $\Delta$(systolic pressure) of the LV ($\Delta_{LVSP}$) and $\Delta$(systolic pressure) of the RV ($\Delta_{RVP}$) during the various experimental conditions. A positive and statistically significant slope was considered the expression of an interaction between the two ventricles, whose gain was indicated by the slope value.

A second analysis was performed to evaluate whether, as in theoretical and experimental studies, the gain of the ventricular interaction depends on the systolic elastance of the interventricular septum (10, 18) and on RV volume (8, 9). To evaluate the effect of septum elastance, we measured the interventricular delay as suggested by Verbeek et al. (25). Indeed, when LBBB is present, septum contraction starts, and consequently ends, before that of the lateral wall; as a consequence, septum elastance might already be decreasing when systolic ventricular pressure, generated by the lateral wall, is just rising; this would explain the systolic stretching of the septum observed in this situation (26) and how the activation delay of the lateral wall influences systolic septal elastance (10). Since the delay between the lateral wall and the septum cannot be obtained directly from the pressure curves of the two ventricles, we employed interventricular delay as its surrogate. Delays in the ascending slope of the two pressure curves were thus measured by the cross correlation technique, at the shortest (60–80 ms) and at the longest (140–160 ms) A-LV delay available for each patient. Then, from absolute values shorter than 15 ms and longer than 25 ms, a two-level (short, long) categorical coding variable ($D$) was derived. We expected the group of observations with short delay to have a better septum-to-lateral wall synchrony (which should translate in a higher LV dP/dtmax) and therefore a reduced ventricular interaction gain.

To evaluate the dependence of the gain of ventricular interaction on RV end-diastolic volume (EDV), the latter was assessed by the natural logarithm of RV end-diastolic pressure [ln(RVDP), see DISCUSSION]. Any relevant colinearity between $\Delta$ln(RVDP) and systolic pressure in the RV was looked for, and excluded, by a mixed regression analysis; a four-value categorical coding variable ($Q$) was then built to identify measurements associated with the first (I), second (II), third (III), and fourth (IV) quartiles of the $\Delta$ln(RVDP) distribution. A greater interaction gain was expected in the groups of measurements identified by higher quartiles of $\Delta$ln(RVDP).

Statistical analysis. For statistical analysis, we used both MlwiN and Systat 12 commercial packages. Best values of the hemodynamic variables obtained with synchronous biventricular stimulation were compared with those at baseline by the Student’s $t$-test for paired data, with significance level set at $P \leq 0.05$. Other mean values were compared by a two-sample $t$-test. If more than two values were to be compared, a preliminary ANOVA and, subsequently, Bonferroni’s correction were applied. Mixed regression analysis for hierarchical data was used to assess the relationship between the dependent and the predictor variables, with observation at the first ($i$) and patient at the second ($j$) level in the following equation:

$$y_{ij} = \beta_0 + \beta_1 x_{ij} + e_{ij}$$

where $y_{ij}$ and $x_{ij}$ are the values of the dependent and predictor variables, respectively; $\beta_0$ is the estimate of the mean intercept; $\beta_1$ is the estimate of the mean slope of the regression; and $e_{ij}$ is the measurement error. The null hypothesis (i.e., $\beta_0 = 0$ and $\beta_1 = 0$) was rejected if the ratio between the mean estimates and their standard error (SE) corresponded to a probability $<0.05$ in the two-tailed $Z$ distribution. The $\chi^2$ probability value associated with the difference in the log likelihood ratio was used to assess the performance of models in which random effects were added or removed to the parameters of Eq. 1. Categorical variables were then separately added to the first equation, as fixed effects interacting with changes in LV systolic pressure. Also in this case, statistic significance was assessed by the $Z$ distribution of the ratio between effects and their SE.

RESULTS

Resynchronization effects. The baseline values and the means of all values with biventricular pacing in the whole data set are depicted in Table 1: in the LV, systolic variables increased whereas end-diastolic pressure (LVEDP) did not vary; no substantial changes were recorded in the RV. However, the best results chosen on the basis of LV dP/dtmax were as expected (24); LV dP/dtmax increased by 34 ± 20% ($P < 0.01$), while LVEDP decreased by 14 ± 14% ($P < 0.01$); also in this case, values for the RV did not change significantly with respect to baseline.

Interaction analysis. Results of the mixed regression analysis between changes in RV and LV pressures over the whole data set (369 measures) are presented in Table 2. Adding the random component to the equation affected the intercept, but

<table>
<thead>
<tr>
<th>EF, %</th>
<th>LVEDd, mm</th>
<th>$p$V$O_2$, ml kg$^{-1}$·min$^{-1}$</th>
<th>LVSP, mmHg</th>
<th>RVSP, mmHg</th>
<th>LVEDP, mmHg</th>
<th>RVEDP, mmHg</th>
<th>LV dP/dt, mmHg·s$^{-1}$</th>
<th>RV dP/dt, mmHg·s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base</td>
<td>29 ± 8</td>
<td>64 ± 11</td>
<td>10.2 ± 2.6</td>
<td>117 ± 15</td>
<td>35 ± 19</td>
<td>20 ± 16</td>
<td>6 ± 3</td>
<td>985 ± 128</td>
</tr>
<tr>
<td>Pace</td>
<td>0.05</td>
<td>126 ± 13</td>
<td>32 ± 17</td>
<td>20 ± 16</td>
<td>5 ± 2</td>
<td>1,162 ± 156</td>
<td>337 ± 170</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are mean ± SE values at baseline (Base) and with biventricular pacing (Pace) (whole data set). LV, left ventricle; RV, right ventricle; LVEDd, LV end-diastolic diameter; $p$V$O_2$, oxygen consumption at peak exercise; LVSP, LV systolic pressure; RVSP, RV systolic pressure; LVEDP, LV end-diastolic pressure; RVEDP, RV end-diastolic pressure; LV dP/dt, LV maximum change in pressure over time; RV dP/dt, RV maximum dP/dt; NS, not significant.
LV dP/dt

As shown in Fig. 2 and Table 2, the short delay group was (range 26–67 ms); the difference was significant (value for the short delay group of measurements was 8 value of the parameter; SE, standard error of the estimate; Z, ratio between estimate and its standard error; categorical variables compared; variable; short, short delay group; long, long delay group; I, II, III, IV, quartiles of the difference from basal; level 1 (single observation) predictor; j, level 2 (patient) predictor; Dij, mean regression intercept; Dij, mean regression slope; Qij, LV systolic pressure difference from basal; eij, measurement error; D, delay categorical variable; Q, change in natural logarithm of end-diastolic RV pressure [ln(RDP)] categorical variable; short, short delay group; long, long delay group; I, II, III, IV, quartiles of the ln(RDP) distribution.

Data are results of mixed regression analysis. Model, mixed regression equation applied; Parameter, values calculated by the equation; Estimate, calculated value of the parameter; SE, standard error of the estimate; Z, ratio between estimate and its standard error; p1, parameter statistical significance against 0; Contrast, categorical variables compared; p2, statistical significance of the difference between categorical variables; ΔRVSP, RV systolic pressure difference from basal; i, j, index, level 1 (single observation) predictor; j, level 2 (patient) predictor; Dij, mean regression intercept; Dij, mean regression slope; Qij, LV systolic pressure difference from basal; eij, measurement error; D, delay categorical variable; Q, change in natural logarithm of end-diastolic RV pressure [ln(RDP)] categorical variable; short, short delay group; long, long delay group; I, II, III, IV, quartiles of the ln(RDP) distribution.

Effects of right diastolic pressure. The mean value of RV diastolic pressure was 6 ± 3 mmHg (range 0–12 mmHg); the ln(RDP) range was 0.038–2.46 mmHg. The four quartiles for Δln(RDP) were 1.156 ± 0.553, −0.278 ± 0.068, 0.072 ± 0.135, and 0.638 ± 0.219, respectively; their differences were significant (P < 0.0001). No significant relation was evident between Δln(RDP) and changes in systolic pressure in the RV. The slope of the regression according to the quartiles (Table 2 and Fig. 3) did not differ from 0 at the first quartile but were progressively higher and statistically different from 0 at the other quartiles. Finally, each slope except the second and the third was also significantly different from the others.

Table 2. Results of mixed regression analysis

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>Z</th>
<th>p1</th>
<th>Contrast</th>
<th>p2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔRVSP = β0 + β1 ΔLVSP + eij</td>
<td>β0</td>
<td>−1.898</td>
<td>0.695</td>
<td>2.73</td>
<td>0.006</td>
<td>Short vs. long</td>
<td>0.001</td>
</tr>
<tr>
<td>ΔRVSP = β0 + β1 ΔLVSP + ΔLVSPDj + eij</td>
<td>β0</td>
<td>−1.514</td>
<td>0.785</td>
<td>1.93</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔRVSP = β0 + β1 ΔLVSP + ΔLVSPQj + eij</td>
<td>β0</td>
<td>−1.737</td>
<td>0.728</td>
<td>2.39</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

This study unveiled the influence of ventricular interaction on the behavior of systolic pressure in the RV in patients with...

Fig. 1. Changes in right ventricular (RV) systolic pressure (ΔRVSP) plotted against changes in left ventricular (LV) systolic pressure (ΔLVSP). Open circles, single observations; aligned gray circles, predicted values for each single patient; black line, mean regression line. The predicted values for each patient have different intercepts but similar slopes.

Fig. 2. Values for the categorical variable (short, long) interventricular delay; hatched columns, short delay; filled columns, long delay; bars = SE. Left: slope values; figures inside the columns indicate statistical significance against 0. n.s., Not significant. Right: LV change in pressure over time (dP/dt) values. Values at top indicate statistical significance of the differences between short and long delay. It is evident that short delay is associated with higher LV dP/dt and no evidence of ventricular interaction, whereas at long delay LV dP/dt is lower and a ventricular interaction can be documented.
dilated cardiomyopathy. This result has been achieved by analyzing the linear relationship between changes in individual ventricular systolic pressure elicited by biventricular pacing with different timing to each ventricle. In the following discussion we address three main topics: 1) the use of a linear relationship instead of the crude ratio between pressures; 2) the possible confounding effects of other variables that can influence RV systolic pressure; and 3) the effects of two factors known to influence the ventricular interaction.

Use of a linear relationship. In animal models, a sudden modification of systolic pressure in one ventricle induces a simultaneous change of systolic pressure in the other ventricle. The gain of this “ventricular interaction” is calculated as the ratio between the changes in the pressure values (5, 8, 12). For instance, the gain of the left-to-right systolic interaction is the ratio between changes in the systolic pressure of the two ventricles (right/left) in the beat in which an acute rise in LV pressure is provoked by a sudden aortic occlusion. Since such abrupt pressure modification within a single beat cannot be obtained in human beings, we settled on the steady-state pressure-volume relationship, which can modify the position of the diastolic pressure-volume curve (16). We did not take into consideration the parameters of Eq. 2 describing the pressure-volume relationship, which can modify the position and/or the shape of the diastolic pressure-volume curve. However, passive diastolic properties of the LV (namely end-diastolic stiffness) do not change after acute (14) or chronic (6 mo) biventricular stimulation (22); even if there are no available data on RV diastolic properties after biventricular pacing, we assumed that they did not change as well. In conclusion, given the constancy of diastolic parameters, changes in ln(RDP) should linearly represent changes in EDV, at least in the single patient. A feeble but not significant relationship between ln(RDP) and the associated Δ(systolic pressure) in the RV was found. Thus the influence of the EDV of the RV on its systolic pressure was not of paramount importance in these experiments even though, as shown below, it influenced the ventricular interaction slope.

Confounding effects of other variables. In a 30-s time span, the one we used for pressure averaging, other factors unrelated to ventricular interaction could come into play and change the right ventricular systolic pressure in a way consistent with the left. Hence, any possible interference with the determinants of end-systolic ventricular pressure, to which maximum systolic pressure is linearly related (4), should be examined. In the framework of ventricular arterial coupling analysis (1, 23), end-systolic pressure in a ventricle (PEs) is determined by the interplay between its end-diastolic volume (EDV), the unstressed volume (V0), end-systolic elastance (Ees), and the apparent elastance of the arterial tree (Ea), as shown in Eq. 2:

\[ P_{es} = (EDV - V_0)E_{es} \times E_a/E_{es} + E_a \]  

(2)

Regarding the terms of Eq. 2, apparent arterial elastance (Ea) is mainly related to the vascular resistance and to the heart period (3): the former is not supposed to change consistently in the systemic and pulmonary vascular tree within a 30-s time span; the second was purposely maintained constant over all of the experiment. EDV of the RV is a potential confounding factor, since it can change in a short time because of the variable filling period allowed by different pacing intervals and thus influence systolic pressure changes through a direct effect and/or by increasing the gain of ventricular interaction (8, 9). EDV was not directly measured in our patients, but it was estimated from the natural logarithm of end-diastolic pressure: such a method was justified by the well-known exponential shape of the diastolic pressure-volume curve (16). We did not take into consideration the parameters of Eq. 2 describing the pressure-volume relationship, which can modify the position and/or the shape of the diastolic pressure-volume curve.
The acute modification of end-systolic ventricular elastance is related to acute changes in ventricular contractility (15); the latter can be estimated by changes in the maximum systolic dP/d\(v_{\text{max}}\). In our experiments, dP/d\(v_{\text{max}}\) of the LV, and hence its \(E_{\text{es}}\), were influenced by the different pairs of stimulation intervals used according to the level of resynchronization achieved, and the systolic pressure changed consistently. In contrast, in the RV changes in the systolic pressure did not bear any relationship to the relative dP/d\(v_{\text{max}}\).

In conclusion, none of the above factors, whether or not they influenced the systolic pressure in the LV, seemed to have affected the behavior of the systolic pressure in the right side of the heart, whose changes can be explained instead by the presence of left-to-right interaction.

Factors known to influence ventricular interaction. The influence of both septal elastance and RV volume on the interaction gain have been theoretically explained—in terms of a three-compartment elastance model (18) and nonlinearity of the end-systolic pressure-volume relationship (8)—and experimentally documented (10, 21). The ability to independently stimulate the RV and LV gave us the opportunity to modulate septal elastance through changes in A-LV delay and RV EDV through A-RV delay. The effects of septal elastance on ventricular interaction have been evaluated by comparing the slope of the relation \(\Delta P_{\text{RV}}/\Delta P_{\text{LV}}\) in two groups of measurements, with short (<15 ms) and long (>25 ms) interventricular delays, respectively. These cutoff values were derived from a previous report (26) showing that at an interventricular delay of \(\pm 19\) ms the best resynchronization can be achieved through biventricular pacing in patients with LBBB. Our data, too, are consistent with a better resynchronization at short interventricular delays (mean value \(\pm 10\) ms), when we obtained a higher LV dP/d\(v_{\text{max}}\). With short delays, and hence with better synchrony, septal elastance reaches its maximum level at the time of lateral wall contraction, therefore hindering pressure transmission between the two ventricles. On the contrary, when the septum is out of phase with respect to the left lateral wall, as in the long delay group, its elastance, being low during LV pressure rise, allows a better pressure transmission. This was shown by the different slope values obtained in the two situations paralleling the influence of septal elastance observed in other experimental models (21).

Also, RV EDV, as estimated from \(\Delta n_{\text{RDP}}\), influences the gain of ventricular interaction; indeed, no interaction at all was evident at its lowest values, whereas at the highest RV EDV the interaction slope reached a value very similar to the gain observed in explanted hearts from severe heart failure patients (20). Our finding is in line with the theoretical approach of Dickstein et al. (8), from which a gain equal to zero can be expected at the lowest RV volumes. It is tempting to speculate that the nonlinear behavior we observed at higher RV volumes (see Fig. 3) was also the effect of the nonlinearity of the preload dependence of the pressure-volume relationship.

In conclusion, the linear relationship we found between systolic pressure changes in the two ventricles of patients with dilated cardiomyopathy during biventricular pacing could be explained in terms of ventricular interaction. This interaction, as shown by the analysis of the whole database, can be totally absent or, on the contrary, may have a high gain. The phenomenon of ventricular interaction should be taken into account by the clinical electrophysiologist when looking for optimal interventricular intervals in the setting of biventricular stimulation.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES


