Quantification of left ventricular mechanical dyssynchrony by conductance catheter in heart failure patients

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Steendijk, Paul, Sven A. F. Tulner, Jan J. Schreuder, Jeroen J. Bax, Lieselot van Erven, Ernst E. van der Wall, Robert A. E. Dion, Martin J. Schalij, and Jan Baan. Quantification of left ventricular mechanical dyssynchrony by conductance catheter in heart failure patients. Am J Physiol Heart Circ Physiol 286: H723–H730, 2004.—Mechanical dyssynchrony is an important codeterminant of cardiac dysfunction in heart failure. Treatment, either medical, surgical, or by pacing, may improve cardiac function partly by improving mechanical synchrony. Consequently, the quantification of ventricular mechanical (dys)synchrony may have important diagnostic and prognostic value and may help to determine optimal therapy. Therefore, we introduced new indexes to quantify temporal and spatial aspects of mechanical dyssynchrony derived from online segmental conductance catheter signals obtained during diagnostic cardiac catheterization. To test the feasibility and usefulness of our approach, we determined cardiac function and left ventricular mechanical dyssynchrony by the conductance catheter in heart failure patients with intraventricular conduction delay (n = 12) and in patients with coronary artery disease (n = 6) and relatively preserved left ventricular function. The heart failure patients showed depressed systolic and diastolic function. However, the most marked hemodynamic differences between the groups were found for mechanical dyssynchrony, indicating a high sensitivity and specificity of the new indexes. Comparison of conductance catheter-derived indexes with septal-to-lateral dyssynchrony derived by tissue-Doppler velocity imaging showed highly significant correlations. The proposed indexes provide additional, new, and quantitative information on temporal and spatial aspects of mechanical dyssynchrony. They may refine diagnosis of cardiac dysfunction and evaluation of interventions, and ultimately help to select optimal therapy.

ventricular function

IN ADDITION TO INTRINSIC MYOCARDIAL abnormalities and abnormal loading conditions, cardiac dysfunction in heart failure patients is determined by mechanical nonuniformities (dyssynchrony), which lead to inefficient pump performance and energy expenditure. There is increasing evidence that pharmacological, surgical and pacemaker therapies of heart failure partly exert their beneficial effects by reducing left ventricular (LV) dyssynchrony. Consequently, quantification of LV dyssynchrony will provide diagnostic and prognostic data, which would help to select and guide therapy. Currently, various indexes based on magnetic resonance imaging or echocardiographic measurements are being used. In the present study, we introduce indexes that quantify temporal and spatial aspects of dyssynchrony based on measurements obtained during cardiac catheterization with the use of conductance catheter methodology. To test the feasibility and usefulness of our approach we compared data from congestive heart failure (CHF) patients with left bundle branch block (LBBB) with those from patients with coronary artery disease (CAD) who had relatively preserved LV function. In addition, we compared the conductance catheter-derived dyssynchrony indexes with septal to lateral delay in peak systolic velocity as obtained by tissue-Doppler imaging.

METHODS

Patients

All patients gave informed consent to participate in the study, and the procedures were conducted in accordance with institutional guidelines. The investigation conforms to the principles outlined in the Declaration of Helsinki (34). Twelve CHF patients (New York Heart Association class III/IV) with LBBB were studied during diagnostic catheterization. Six CAD patients were studied in the operating room before undergoing coronary artery bypass grafting.

Protocol

CHF patients underwent diagnostic catheterization, including thermodilution cardiac output, left ventriculography, and coronary angiography. In addition, a conductance catheter was placed in the LV via the femoral artery, and a temporary pacing lead was positioned in the right atrium.

Before catheterization, the CHF patients were studied by echocardiography. We performed tissue-Doppler imaging as described in detail elsewhere (3) to determine myocardial velocities in basal septal and lateral segments. The time delay between peak systolic velocity in the septum and the lateral wall was determined as an index of mechanical dyssynchrony.

CAD patients received total intravenous anesthesia with target-controlled infusion of propofol and remifentanil (1.5–2 μg/ml, respectively, 5–10 ng/ml blood concentration). A continuous cardiac output catheter was placed in the pulmonary artery via the jugular vein. After a midline sternotomy and before cardiopulmonary bypass was started, a conductance catheter was placed in the LV via a purse-string suture on the ascending aorta. External pacing leads were placed on the right atrium.

Measurements. The conductance catheter enables online measurement of five segmental volume (Vseg,i) slices perpendicular to the LV long axis. We used 7-Fr combined pressure-conductance catheters with 1-cm interelectrode spacing (CD Leycom; Zoetermeer, the Netherlands). The catheter was connected to a Cardiac Function Lab (CD Leycom) for online display and acquisition (sample frequency 250 Hz) of segmental and total LV volumes, LV pressure, and ECG.

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Total LV volume ($V_{LV}$) is obtained as the instantaneous sum of the segmental volumes. $V_{LV}$ was calibrated using thermodilution and hypertonic saline dilution, as previously described (2). Periods of ~10 s at a paced heart rate of 80 beats/min were selected for off-line analysis using custom-designed software.

Global cardiac function and nonuniform mechanical performance. Global LV function was measured by cardiac index (CI), end-diastolic and end-systolic volume index (EDVI and ESVI), ejection fraction (EF), end-systolic and end-diastolic pressure (ESP and EDP), maximal and minimal rate of pressure change ($dP/dt_{max}$ and $dP/dt_{min}$), and the time constant of relaxation ($\tau$). LV systolic elastance was estimated by ESP/ESVI and ($dP/dt_{max}$)/EDVI was calculated as a relatively load-independent index of systolic function.

Nonuniform LV performance was determined from the segmental LV conductance signals and characterized by the following indexes.

Mechanical dyssynchrony. At each time point, a segmental signal was defined as dyssynchronous if its change (i.e., $dV_{seg}/dt$) was opposite to the simultaneous change in the total LV volume ($dV_{LV}/dt$). Segmental dyssynchrony is quantified by calculating the percentage of time within the cardiac cycle that a segment is dyssynchronous. Overall LV dyssynchrony (DYS) was calculated as the mean of the segmental dyssynchronies (23). DYS may be calculated within each specified time interval: we determined DYS during systole (DYSs) and diastole (DYSd), with systole defined as the period between the moments of $dP/dt_{max}$ and $dP/dt_{min}$.

Internal flow. Nonuniform contraction and filling is associated with ineffective shifting of blood volume within the LV. This internal flow (IF) is quantified by calculating the sum of the absolute volume changes of all segments and subtracting the absolute total volume change: $IF(t) = 2\sum|dV_{seg}(t)/dt| - |dV_{LV}(t)/dt|/2$. Note that $dV_{LV}(t)/dt$ represents the effective flow into or out of the LV. Thus IF measures the segment-to-segment blood volume shifts, which do not result in effective filling or ejection. Division by two takes into account that any noneffective segmental volume change is balanced by an equal but opposite volume change in the remaining segments. IF fraction (IFF) is calculated by integrating IF over the full cardiac cycle and dividing by the integrated absolute effective flow.

Mechanical dispersion. In the CHF patients, we expected a substantial dispersion in the onset of contraction between the segments. This dispersion was assessed by segmental lag times, $t_{lag,i}$, which were determined by calculating the cross correlations between $V_{LV}(t)$ and $V_{seg}(t + t_{lag,i})$ for all systolic time points (i.e., between $dP/dt_{max}$ and $dP/dt_{min}$). For each segment we determined the $t_{lag,i}$, which produced the highest linear correlation. Thus if $t_{lag,i} < 0$, segment i precedes the global ejection and vice versa. Mechanical dispersion (DISP) was defined as 2 SD of the segmental lag times.

### Statistical Analysis

All data are presented as means ± SD. Comparisons between the CAD and CHF groups were performed by unpaired $t$-tests. We performed receiver-operating characteristic (ROC) curve analysis to test the diagnostic performance of the various indexes to discriminate the patient groups (38). Sensitivities and specificities at the optimal cutoff point were determined. Comparison between conductance-derived and tissue-Doppler-derived dyssynchrony indexes was made by linear regression analysis.

### RESULTS

Typical pressure-volume loops from a CAD and a CHF patient are shown in Fig. 1. The bottom panel shows the global LV pressure-volume loops clearly illustrating enlarged volumes and increased end-diastolic pressure in the CHF patient. Furthermore, whereas the CAD patient displays normal isovolumic trajectories during the contraction and relaxation phases, the loops from the CHF patient show a continued decrease in volume during these phases, presumably reflecting mitral insufficiency. The segmental pressure-volume loops displayed in the top panels illustrate the inefficient ventricular contraction and filling in the CHF patient.
pump behavior of the CHF patient especially in the apical segments. The same signals are also displayed as a function of time in Fig. 2. The top panels show the segmental and total LV volumes and LV pressure. The bottom panels show calculated IFs. Contraction and filling patterns are substantially more dyssynchronous in the CHF patient compared with the CAD patient. In the CAD patient IF is largely restricted to the isovolumic contraction and relaxation periods, which is consistent with normal physiology, because with the mitral and aortic valves closed, LV shape changes result in internal segment-to-segment flow. In contrast, in the CHF patient substantial ineffective IF is present throughout the cardiac cycle.

Hemodynamic data are summarized in Table 1. EF and dP/dt\text{max} indicate more pronounced systolic dysfunction, whereas ESP/ESVI and (dP/dt\text{max})/EDVI show depressed contractile state, whereas τ and EDP indicate impaired diastolic function in CHF. Differences in EDVI, ESVI, and CI were present but did not reach statistical significance. Pronounced differences between CAD and CHF were found in DYS, IFF, and DISP. For both groups, dyssynchrony and IFs were highest in diastole, and the apical segments were the most affected (Fig. 3A). In both groups, mechanical dispersion in the long-axis direction was present, but it was twice as large in CHF. Figure 3B shows that contraction started in the basal segment and, on the average, subsequent segments (1 cm slices), followed by 5.9 ms for CAD and by 12.4 ms in CHF patients.

The diagnostic value of the various indexes to discriminate the two patient groups was tested using ROC analysis. Table 1 shows the results with the optimal cutoff values, and corresponding sensitivities and specificities. As expected, QRS duration accurately delineates the groups with a cut-off value of 107 ms. The dyssynchrony indexes DYS and IFF show excellent sensitivity/specificity values, which are higher than the best hemodynamic indexes EF and dP/dt\text{max}. The other hemodynamic indexes show lower sensitivity/specificity reflecting a substantial overlap of the values between the two groups.

Tissue-Doppler measurements were performed in the CHF patients and revealed a significant difference in the timing of peak systolic velocities of the septum and the lateral wall. The average septal-to-lateral delay was 89 ± 43 ms, indicating a dysynchronous intraventricular contraction pattern. We compared the septal-to-lateral delay times with the conductance-derived dyssynchrony indexes using linear regression analysis. The results (Fig. 4) show highly significant correlations with DYS (r\textsuperscript{2} = 0.59, P = 0.003) and IFF (r\textsuperscript{2} = 0.63, P = 0.002). The relation with DISP did not reach statistical significance (r\textsuperscript{2} = 0.26, P = 0.089).

**DISCUSSION**

Dysynchrony plays a regulating role already in normal physiology (6) but is especially important in pathological conditions, such as hypertrophy (33), ischemia (10), infarction (8), or heart failure (18). Currently, cardiac resynchronization by biventricular pacing is emerging as an important therapy for heart failure (15, 20). Recently, magnetic resonance imaging (18, 36) and echocardiography (1, 5, 13, 25, 37) have been used to visualize mechanical dyssynchrony, further emphasizing the important role of mechanical dyssynchrony in cardiac physiology.
dysfunction. However, these methods are laborious and require substantial operator interaction and expertise.

We introduce novel indexes to quantify dyssynchrony based on volume signals acquired with the conductance catheter during cardiac catheterization. The conductance catheter was validated previously (2), and the segmental signals reflect instantaneous volume slices perpendicular to the LV long axis as obtained by cine-computerized tomography (32). Currently, the conductance catheter is used mainly to assess global systolic and diastolic function (9, 11, 12, 17). Quantification of nonuniform mechanical function and dyssynchrony may lead to a more complete diagnosis of ventricular dysfunction (23, 24). Moreover, it may guide therapy, because patients with extensive dyssynchrony are likely to benefit from resynchronization therapy (15).

We compared CHF versus CAD patients. The groups show pronounced differences for DYS, IFF, and DISP, which indicate a high sensitivity and specificity of these dyssynchrony indexes. QRS duration, dP/dt\(_{\text{max}}\) and \(\tau\) show a similar discrimination between the groups and may also partly reflect dyssynchrony. However, whereas the conductance catheter-derived indexes directly measure regional mechanical events throughout the cardiac cycle, QRS duration reflects the underlying electrical activation, and studies indicate that mechanical and

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**Table 1. Cardiac function, left ventricular mechanical dyssynchrony and ROC curve analysis in CAD and CHF patients**

<table>
<thead>
<tr>
<th>Cardiac Function and Mechanical Dyssynchrony</th>
<th>ROC Curve Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAD (n = 6)</strong></td>
<td><strong>CHF (n = 12)</strong></td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>5/1</td>
</tr>
<tr>
<td>Age, yr</td>
<td>63±7</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>86±16</td>
</tr>
<tr>
<td>CI, l/min(^{-1})m(^{-2})</td>
<td>2.6±0.8</td>
</tr>
<tr>
<td>EDVI, ml/m(^2)</td>
<td>73±33</td>
</tr>
<tr>
<td>ESVI, ml/m(^2)</td>
<td>45±25</td>
</tr>
<tr>
<td>EF, %</td>
<td>48±16</td>
</tr>
<tr>
<td>dP/dt(_{\text{max}}), mmHg/s</td>
<td>1,106±160</td>
</tr>
<tr>
<td>dP/dt(_{\text{min}}), mmHg/s</td>
<td>-1,012±229</td>
</tr>
<tr>
<td>(\tau), ms</td>
<td>58±9</td>
</tr>
<tr>
<td>ESP, mmHg</td>
<td>86±18</td>
</tr>
<tr>
<td>EDVI, mmHg</td>
<td>9±5</td>
</tr>
<tr>
<td>ESP/ESVI, mmHg·ml(^{-1})m(^{-2})</td>
<td>2.7±1.9</td>
</tr>
<tr>
<td>(dP/dt(_{\text{max}}))/EDVI, mmHg·s(^{-1})ml(^{-1})m(^{-2})</td>
<td>17±7</td>
</tr>
<tr>
<td>DYS(_S), %</td>
<td>19±8</td>
</tr>
<tr>
<td>DYS(_D), %</td>
<td>11±11</td>
</tr>
<tr>
<td>IFF(_S), %</td>
<td>24±6</td>
</tr>
<tr>
<td>IFF(_D), %</td>
<td>20±14</td>
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<tr>
<td>IFF, %</td>
<td>13±19</td>
</tr>
<tr>
<td>IFF(_S), %</td>
<td>25±12</td>
</tr>
<tr>
<td>IFF(_D), %</td>
<td>33±13</td>
</tr>
</tbody>
</table>

Values given as means ± SD; n, no. of patients. ROC, receiver-operating characteristic; CI, cardiac index; EDVI, ESVI, end-diastolic and end-systolic volume index; EF, ejection fraction; dP/dt\(_{\text{max}}\) and dP/dt\(_{\text{min}}\), maximal and minimal rate of left ventricular (LV) pressure change; \(\tau\), time constant of relaxation; ESP and EDVI, end-diastolic and end-diastolic pressure; DYS, mechanical dyssynchrony; DYS\(_S\), and DYS\(_D\), systolic and diastolic DYS, respectively; IFF, internal flow fraction; IFF\(_S\) and IFF\(_D\), systolic and diastolic IFF, respectively; DISP, mechanical dispersion. \(P\) values determined by unpaired \(t\)-tests.

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**Fig. 3. Average segmental dyssynchrony (A) and dispersion lag times (B) in CAD and CHF patients. Inset, conductance catheter positioned in the LV and the division in five segments from apex to base.**
Electrical synchrony may diverge (14). τ and dP/dt max have also been shown to be markers of dyssynchrony but they more indirectly reflect the integrated effects of spatially dispersed mechanical (de)activation during the isovolumic relaxation and contraction periods. Dyssynchrony is likely to be most pronounced in the isovolumic phases, which explains the sensitivity of parameters that reflect these periods. However, the consequences of dyssynchrony on the effectiveness of ejection and filling are important for cardiac pump performance, so that indexes selectively reflecting those cardiac phases may be of high value.

In the CHF patients, we compared the conductance-derived dyssynchrony indexes with the delay in timing of peak systolic velocity between the septal and lateral wall as obtained by tissue-Doppler echocardiography. Septal-to-lateral delay has recently been introduced as an index of mechanical dyssynchrony. We found a significant correlation for both DYS and IFF, but DISP did not reach a statistically significant correlation. The various indexes measure different characteristics. Whereas the tissue-Doppler method compares the timing of peak velocity between two regions that are likely to show the largest phase shift, the conductance-derived indexes are based on a comparison of the volume changes of short axis slices and global LV volume changes. Apparently, patients with a larger septal-to-lateral delay also show more segmental dyssynchrony, as reflected by DISP and IFF. It is unknown whether this correspondence is specific for LBBB-CHF patients or is more generally valid. The lack of correlation with DISP is unclear. It may be because the index is less sensitive than DISP or IFF as shown in the comparison between CAD and CHF patients, or the index may inherently be more prone to errors.

Interestingly, within the group of CHF patients, neither septal-to-lateral delay nor the conductance-derived indexes showed a significant correlation with QRS duration (Fig. 5). This finding is consistent with other reports (14, 18) indicating that electrical dyssynchrony does not necessarily predict mechanical dyssynchrony, which prompts a need for methods to accurately detect mechanical dyssynchrony.

Our approach may offer several technical advantages. After catheter placement, the signals are obtained continuously without operator interaction. In the present study, the analysis was performed off-line, but real-time display of dyssynchrony indexes is technically feasible and should enable immediate quantification of the effects of interventions, and, e.g., the effects of changes in pacemaker settings. The method is invasive, but positioning of the catheter in the LV largely eliminates problems with through-plane motion inherent in most imaging methods. Heart failure is often associated with substantial beat-to-beat hemodynamic variations due to changes in cycle length, cardiopulmonary interaction and conduction disturbances. Thus techniques (like magnetic resonance imaging) that require hemodynamic steady-state and beat averaging to increase signal-to-noise may filter out important components of dyssynchrony. Furthermore, the temporal resolution of the conductance signals (4 ms) is relatively high.

Determination of absolute LV volume from the conductance catheter requires careful calibration (2). In the present study, calibration factor parallel conductance was obtained by the hypertonic saline method and slope factor - by thermodilution. Slope factor - was significantly lower in the CHF patients than in the CAD patients (0.38 ± 0.22 vs. 0.67 ± 0.08, P < 0.01), and parallel conductance was significantly higher (214 ± 60
vs. 131 ± 48 ml; \( P < 0.01 \)). These findings are consistent with previous studies and reflect more electrical field inhomogeneity in the enlarged hearts in the CHF group. However, the conductance catheter has been used extensively in enlarged hearts, and validation studies show that accurate volumes estimates can be obtained, provided that the appropriate calibration is performed (19). Another advantage is that the dyssynchrony indexes can be calculated from the raw segmental conductance signals and do not require calibration. Correction for parallel conductance (offset factor) is not required because the calculations are based on volume changes, and correction for slope factor-\( \alpha \) is not required because segmental volume changes are judged relative to the global LV volume changes. The latter, however, implicitly assumes that the segmental slope factors are all the same (and thus equal to the slope factor for global volume). This assumption may be a concern because theoretical studies indicate that volume in the segments closest to the current electrodes may be relatively underestimated due to electric field inhomogeneity, especially in enlarged hearts (26, 27, 35). To test the effects of such underestimations, if present, on our dyssynchrony indexes we recalculated DYS, IFF, and DISP after correcting segments 1 and 5 for an assumed underestimation of 20% and segments 2 and 4 for an assumed underestimation of 10%. Theoretical studies indicate that underestimation in this order of magnitude may be present (26, 35). The results were compared with the original data using Bland-Altman analysis (4) (Fig. 6). The analysis shows no significant bias and fairly narrow limits of agreement for each of the indexes, indicating that the influence of a potential underestimation of the outer segments on the dyssynchrony indexes is relatively small. Although the mean dyssynchronies were higher in the CHF patients, the differences as detected by the Bland-Altman analysis were not systematically different between the two groups.

The methods for quantifying dyssynchrony presented in this study show similarities with an approach previously published by Strum and Pinsky (29). They used segmental volume signals obtained from conductance catheters to quantify regional wall motion abnormalities and referenced amplitudes and phase angles of the segmental signals to the global LV volume signal. The phase angle analysis is comparable to our IFF calculation (IFF index), which determines at each time point throughout the cardiac cycle whether segmental volume changes are effective (i.e., contributing to global volume changes) or lead to ineffective (segment to segment) IF. Strum and Pinsky (28, 30) applied these concepts in animal studies where reversible regional myocardial dysfunction was induced by intracoronary infusion of esmolol and global inotropy was modulated by dobutamine infusions.

**Limitations**

Optimally, the conductance catheter is placed in a straight position from the aortic valve to the LV apex. In the operating room, we used transesophageal echocardiography (31) and in the catheterization laboratory, we used angiography to guide positioning. However, occasionally arrhythmias necessitate pulling back the catheter slightly from the apical position. In addition, the distance from the pigtail to the first measurement electrode is ~2 cm. Thus volume changes in the most apical part of the LV are not measured. If this region is highly dyssynchronous, as might be the case in patients with apical infarcts, underestimation of dyssynchrony by our methodology may be expected.

The patient groups in our study were investigated under different conditions. For practical purposes, we studied the CAD patients in the operating room during anesthesia and after sternotomy, whereas the CHF patients were awake and studied in the catheterization laboratory. These differences may have affected the comparisons between the two groups. Propofol-remifentanyl anesthesia is known to have myocardial depressant and vasodilating properties (16, 22), whereas sternotomy and pericardiectomy are associated with alterations in loading conditions (7). Given the anesthesia-related cardiodepression in the CAD patients, one may expect that the differences in the hemodynamic indexes would have been more pronounced in case both groups had been studied awake. Whether these changes affect the level of dyssynchrony is not well known, but studies in dogs with regional stunning show unchanged LV wall asynchrony after systemic inotropic stimulation (21). Thus we do not expect that the differences in mechanical dyssynchrony between the groups were importantly influenced by the different experimental conditions.

**Fig. 6.** Bland-Altman analysis comparing conductance catheter-derived indexes of mechanical dyssynchrony before and after correction of assumed underestimation of segmental volumes due to electric field inhomogeneity. ○, CHF patients; ●, CAD patients. A: DYS (%); B: IFF (%); C: DISP (ms).

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Furthermore, we did not study normal subjects. Thus future studies are required to establish a normal range for the diysynchrony indexes.

Finally, the segmental conductance catheter signals do not provide an anatomic view but represent the total volume of slices perpendicular to the LV long axis. Thus, e.g., in CAD patients, abnormal regional wall motion might be obscured by compensatory wall motions within the same circumferential segment. The proposed diysynchrony indexes therefore reflect intersegmental differences in contraction and filling and may underestimate phase changes obtained by comparing regional lateral and septal wall motions, e.g., using tissue Doppler imaging.

In conclusion, the proposed indexes quantify various aspects of mechanical diysynchrony using conductance catheter methodology, which, at the same time, can be used for assessment of global systolic and diastolic (dy)sfunction. Diagnostic and prognostic value of the diysynchrony indexes requires further investigation.

GRANTS
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