# Non-pharmacological heart failure therapies : evaluation by ventricular pressure-volume loops

Tulner, Sven Arjen Friso

# CHAPTER 3

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

**P. Steendijk**
**S.A.F. Tulner**
**J.J. Schreuder**
**J.J. Bax**
**L. van Erven**
**E.E. van der Wall**
**R.A.E. Dion**
**M.J. Schalij**
**J. Baan**

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## ABSTRACT

Mechanical dyssynchrony is an important co-determinant of cardiac dysfunction in heart failure. Treatment, either medical, surgical, or by pacing, may improve cardiac function to a large extent by improving mechanical synchrony. Consequently the quantification of ventricular mechanical dyssynchrony may have important diagnostic and prognostic value and may help to determine optimal therapy. Therefore we introduced new indices to quantify temporal and spatial aspects of mechanical dyssynchrony derived from on-line 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 indices. Comparison of conductance catheter derived indices with septal-to-lateral dyssynchrony derived by tissue-Doppler velocity imaging showed highly significant correlations.

The proposed indices 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.


## INTRODUCTION

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 should help to select and guide therapy.

Currently, various indices based on magnetic resonance imaging or echocardiographic measurements are being used. In the present study we introduce indices, which quantify temporal and spatial aspects of dyssynchrony based on measurements obtained during cardiac catheterization using 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 indices with septal to lateral delay in peak systolic velocity as obtained by tissue-Doppler imaging.

## METHODS

### Patients

All patients gave informed consent and procedures were conducted in accordance with institutional guidelines. The investigation conforms with the principles outlined in the Declaration of Helsinki.[1] Twelve CHF patients (NYHA class III/IV) with LBBB were studied during diagnostic catheterization. Six CAD patients were studied in the operating room prior to 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.

Prior to catheterization the CHF patients were studied by echocardiography. We performed tissue-Doppler imaging as described in detail elsewhere[2] 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 remifentanyl (1.5-2μg/ml, resp. 5-10ng/ml blood concentration). A continuous cardiac output catheter was placed in the pulmonary artery via the jugular vein. Following midline sternotomy and before starting cardiopulmonary bypass 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 on-line measurement of 5 segmental volume ($V_{SEG,i}$) slices perpendicular to the LV long axis. We used 7F 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 on-line display and acquisition (sample frequency 250Hz) of segmental and total LV volumes, LV pressure and ECG. 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.[3] Periods of approximately 10s at a paced heart rate of 80bpm were selected for off-line analysis using custom-made 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, ESVI), ejection fraction (EF), end-systolic and end-diastolic pressure (ESP, EDP), maximal and minimal rate of pressure change ($dP/dt_{MAX}$, $dP/dt_{MIN}$), and the time constant of relaxation (Tau). LV systolic elastance was estimated by ESP/ESVI, and in addition ($dP/dt_{MAX}$)/EDVI was calculated as relatively load-independent index of systolic function.

Nonuniform LV performance was determined from the segmental LV conductance signals and characterized by the following indices:

***Mechanical dyssynchrony (DYS):*** At each time-point a segmental signal was defined as dyssynchronous if its change (i.e. $dV_{SEG}/dt$) was opposite to 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.[4] DYS may be calculated within each specified time-interval: We determined DYS during systole ($DYS_S$) and diastole ($DYS_D$), with systole defined as the period between the moments of $dP/dt_{MAX}$ and $dP/dt_{MIN}$.

***Internal flow (IF):*** Nonuniform contraction and filling is associated with ineffective shifting of blood volume within the LV. This 'internal flow' is quantified by calculating the sum of the *absolute* volume changes of all segments and subtracting the absolute total volume change: $IF(t) = (\Sigma|dV_{SEG,i}(t)/dt| - |dV_{LV}(t)/dt|)/2$. Note that $dV_{LV}(t)/dt$ represents the effective flow into or out of the LV. Thus, IF measures segment-to-

segment blood volume shifts which do not result in effective filling or ejection. Division by 2 takes into account that any 'non-effective' segmental volume change is balanced by an equal but opposite volume change in the remaining segments. Internal Flow Fraction (IFF) is calculated by integrating IF(t) over the full cardiac cycle and dividing by the integrated absolute effective flow.

***Mechanical dispersion (DISP):*** 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 $V_{SEG,i}(t+t_{LAG,i})$ 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 mean±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 indices to discriminate the patient groups.[5] Sensitivities and specificities at the optimal cut-off point were determined. Comparison between conductance-derived and tissue-Doppler derived dyssynchrony indices was made by linear regression analysis.

## RESULTS

Typical pressure-volume loops from a CAD and a CHF patient are shown in Figure 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 pump behavior of the CHF patient especially in the apical segments.

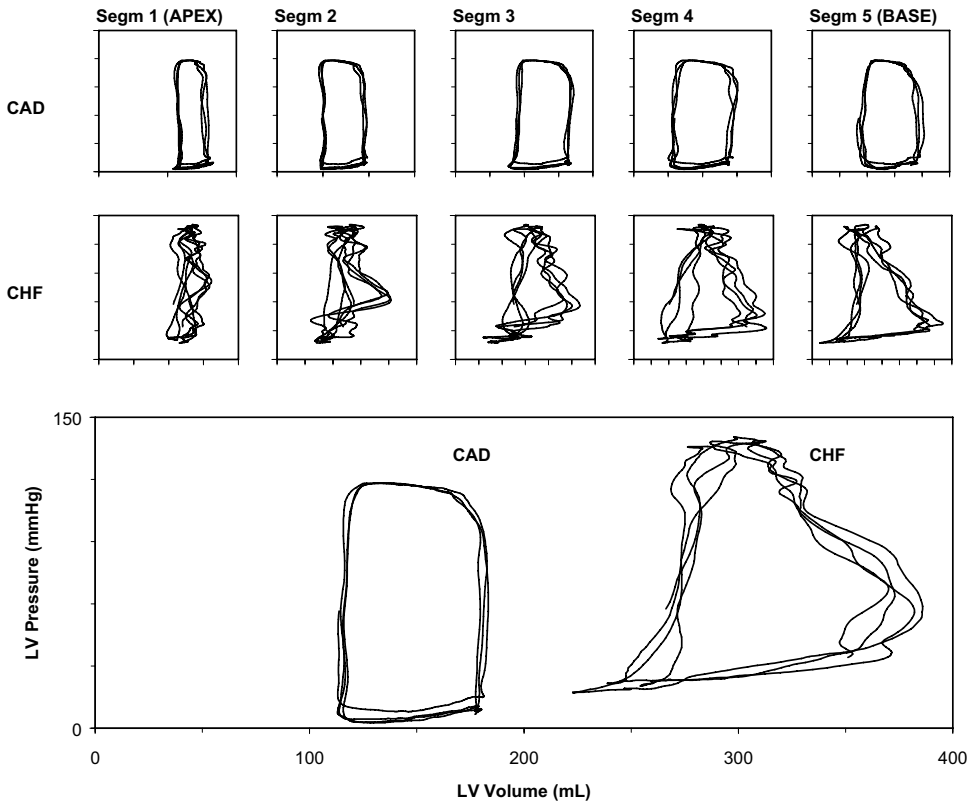


*Figure 1. Segmental and global LV pressure-volume loops in typical CAD and CHF patients*

The same signals are also displayed as a function of time in Figure 2. The top panels show the segmental and total LV volumes, and LV pressure. The bottom panels show calculated internal flows. Contraction and filling patterns are substantially more dyssynchronous in the CHF patient compared to the CAD patient. In the CAD patient internal flow is largely restricted to the isovolumic contraction and relaxation periods, which is consistent with normal physiology since, with mitral and aortic valves closed, LV shape changes result in internal segment-to-segment flow. In contrast, in the CHF patient substantial ineffective internal flow is present throughout the cardiac cycle.

Hemodynamic data are summarized in Table 1. EF and $dP/dt_{MAX}$ indicate more pronounced systolic dysfunction while ESP/ESVI and $(dP/dt_{MAX})$/EDVI show depressed contractile state, whereas Tau 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.

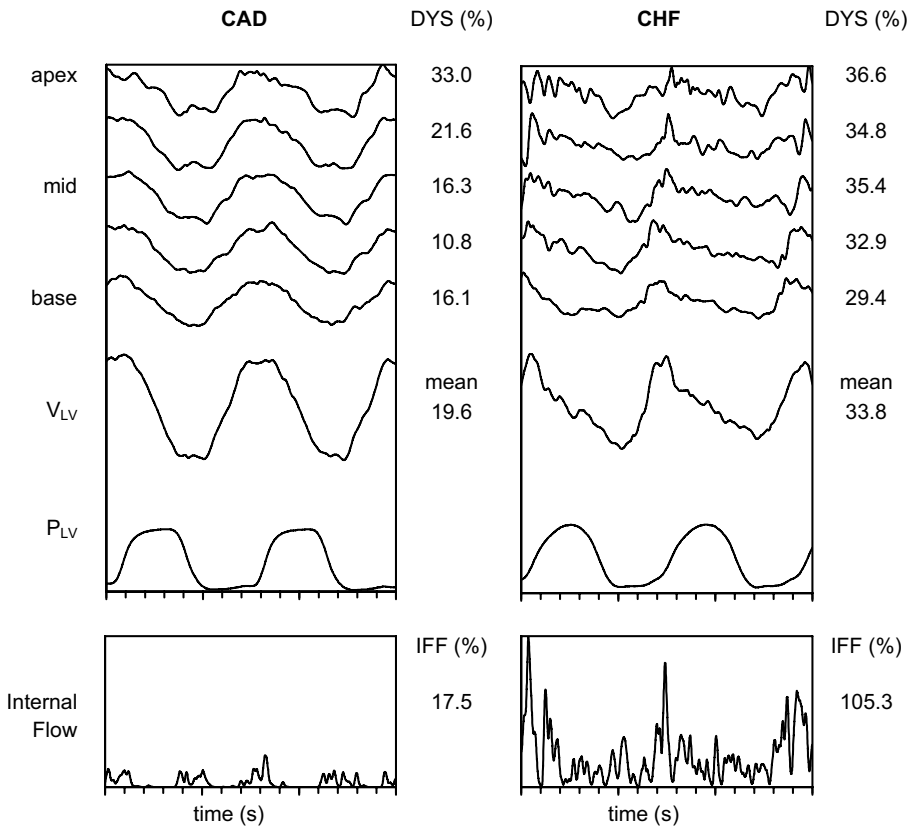


*Figure 2. Typical examples of segmental and total LV volume signals and calculated internal flow in CAD and CHF patients. DYS: mechanical dyssynchrony; IFF: internal flow fraction*

For both groups dyssynchrony and internal flows were highest in diastole, and the apical segments were the most affected (Figure 3). In both groups mechanical dispersion in the long-axis direction was present, but it was twice as large in CHF. Figure 3 (right panel) shows that contraction started in the basal segment and, on the average, subsequent segments (1cm-slices) followed after 5.9ms for CAD and after 12.4ms in CHF patients.

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

*Table 1. Cardiac function, left ventricular mechanical dyssynchrony and receiver-operating characteristic (ROC) curve analysis in CAD (n=6) and CHF (n=12) patients*

| | Cardiac function and mechanical dyssynchrony | | | ROC curve analysis | | |
|---|---|---|---|---|---|---|
| | CAD | CHF | p | cut-off | sensitivity | specificity |
| Gender (M/F) | 5/1 | 9/3 | .709 | | | |
| Age (years) | 63±7 | 67±9 | .399 | | | |
| QRS duration (ms) | 86±16 | 186±24 | <.001 | 107 | 100% | 100% |
| CI (L/min/$m^2$) | 2.6±0.8 | 2.0±0.5 | .099 | 1.88 | 58.3% | 100% |
| EDVI (mL/$m^2$) | 73±33 | 107±37 | .077 | 89 | 58.3% | 83.3% |
| ESVI (mL/$m^2$) | 45±25 | 74±32 | .068 | 58 | 66.7% | 66.7% |
| EF (%) | 48±16 | 26±9 | .001 | 37.6 | 91.7% | 83.3% |
| $dP/dt_{MAX}$ (mmHg/s) | 1106±160 | 764±228 | .005 | 928 | 83.3% | 100% |
| $-dP/dt_{MIN}$ (mmHg/s) | 1012±229 | 827±263 | .164 | 797 | 58.3% | 100% |
| Tau (ms) | 58±9 | 77±16 | .017 | 66.5 | 75% | 100% |
| ESP (mmHg) | 86±18 | 106±32 | .167 | 91 | 75% | 83.3% |
| EDP (mmHg) | 9±5 | 18±8 | .024 | 11.4 | 75% | 83.3% |
| ESP/ESVI (mmHg/mL/$m^2$) | 2.7±1.9 | 1.8±1.0 | .183 | 1.89 | 66.7% | 66.7% |
| $dP/dt_{MAX}$/EDVI(mmHg/s/mL/$m^2$) | 17±7 | 8±4 | .002 | 11.3 | 75% | 83.3% |
| DYS (%) | 19±8 | 32±3 | <.001 | 19.6 | 100% | 83.3% |
| $DYS_S$ (%) | 11±11 | 30±6 | <.001 | 13.9 | 100% | 83.3% |
| $DYS_D$ (%) | 24±6 | 34±2 | <.001 | 25.7 | 100% | 83.3% |
| IFF (%) | 20±14 | 78±24 | <.001 | 47.0 | 91.7% | 100% |
| $IFF_S$ (%) | 13±19 | 63±30 | .002 | 11.3 | 100% | 83.3% |
| $IFF_D$ (%) | 25±12 | 90±29 | <.001 | 33.1 | 100% | 100% |
| DISP (%) | 33±13 | 75±37 | .026 | 39.9 | 83.3% | 80% |

*Values given as mean±SD, p-values determined by unpaired t-tests. CI: cardiac index; EDVI, ESVI: end-diastolic and end-systolic volume index; EF: ejection fraction; $dP/dt_{MAX}$ and $_{MIN}$: maximal and minimal rate of LV pressure change; Tau: time constant of relaxation; ESP, EDP: end-systolic and end-diastolic pressure; DYS: mechanical dyssynchrony; $DYS_S$, $DYS_D$: systolic and diastolic DYS; IFF: internal flow fraction; $IFF_S$, $IFF_D$: systolic and diastolic IFF, DISP: mechanical dispersion*

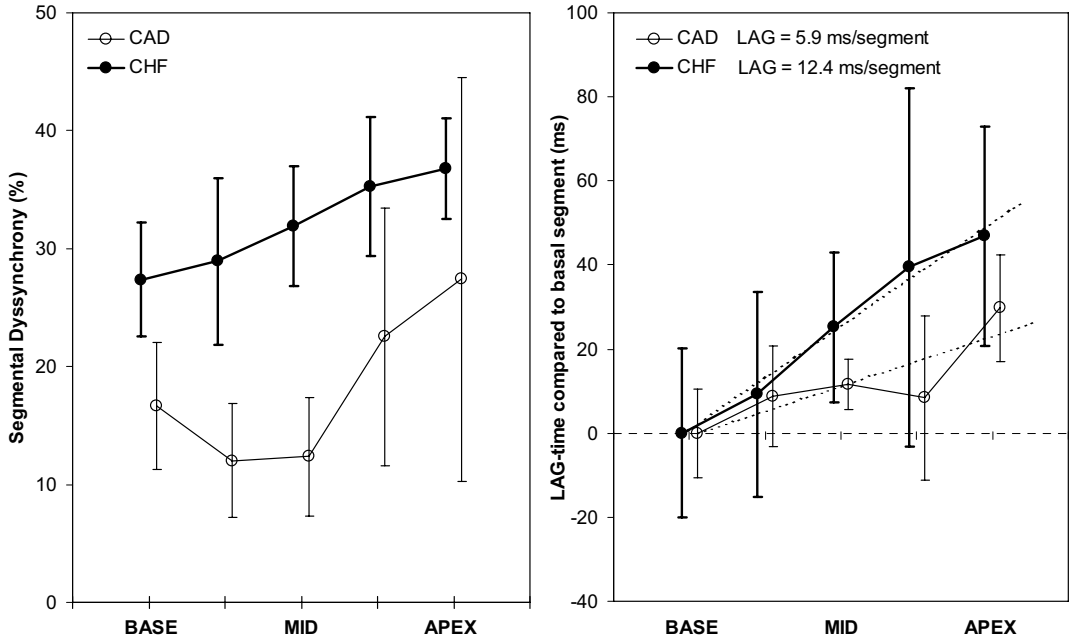


*Figure 3. Average segmental dyssynchrony and dispersion lag-times in CAD and CHF patients. The inset shows the conductance catheter positioned in the LV and the division in 5 segments from apex to base*

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 dyssynchronous intraventricular contraction pattern. We compared the septal-to-lateral delay times with the conductance derived dyssynchrony indices using linear regression analysis. The results (Figure 4) show highly significant correlations with DYS ($r^2$=0.59, p=0.003) and IFF ($r^2$=0.63, p=0.002). The relation with DISP did not reach statistical significance ($r^2$=0.26, p=0.089).

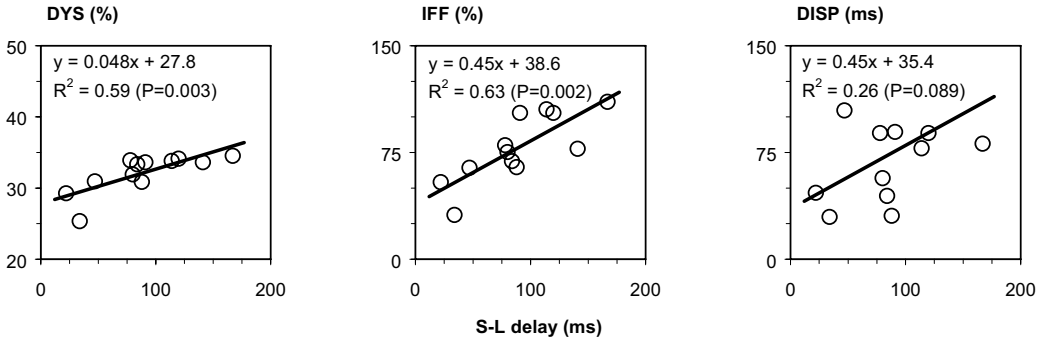


*Figure 4. Linear regression of conductance catheter derived indices of mechanical dyssynchrony (DYS: mechanical dyssynchrony; IFF: internal flow fraction; DISP: mechanical dispersion) versus septal-to-lateral (S-L) delay in the timing of peak systolic myocardial velocity as obtained by tissue-Doppler echocardiography*

## DISCUSSION

Dyssynchrony plays a regulating role already in normal physiology, but is especially important in pathological conditions such as hypertrophy, ischemia, infarction, or heart failure.[6,7,8,9,10] Currently, cardiac resynchronization by biventricular pacing is emerging as an important therapy for heart failure.[11,12] Recently, MRI and echocardiography have been used to visualize mechanical dyssynchrony, further emphasizing the important role of mechanical dyssynchrony in cardiac dysfunction.[10,13,14-18] However, these methods are laborious and require substantial operator interaction and expertise.

We introduce novel indices to quantify dyssynchrony based on volume signals acquired with the conductance catheter during cardiac catheterization. The conductance catheter was validated previously and the segmental signals reflect instantaneous volume slices perpendicular to the LV long-axis as obtained by cine-CT.[3,19] Currently, the conductance catheter is used mainly to assess global systolic and diastolic function.[20-23] Quantification of nonuniform mechanical function and dyssynchrony may lead to a more complete diagnosis of ventricular dysfunction.[24,25] Moreover, it may guide therapy, since patients with extensive dyssynchrony are likely to benefit from resynchronization therapy.[26]

We compared CHF versus CAD patients. The groups show pronounced differences for DYS, IFF and DISP, which indicates a high sensitivity and specificity of these dyssynchrony indices. QRS duration, $dP/dt_{MAX}$ and Tau show a similar discrimination between the groups and may also partly reflect dyssynchrony. However, whereas the conductance catheter derived indices directly measure regional mechanical events throughout the cardiac cycle, QRS duration reflects the underlying electrical activation and studies indicate that mechanical and electrical synchrony may diverge.[27] Tau 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 indices selectively reflecting those cardiac phases may be of high value.

In the CHF patients we compared the conductance derived dyssynchrony indices 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 indices 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 indices 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. Whether this correspondence is specific for LBBB-CHF patients or is more generally valid requires further study. 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 indices showed a significant correlation with QRS duration (Figure 5). This finding is consistent with other reports indicating that electrical dyssynchrony does not necessarily predict mechanical dyssynchrony, which prompts a need for methods to accurately detect mechanical dyssynchrony.[10,28]

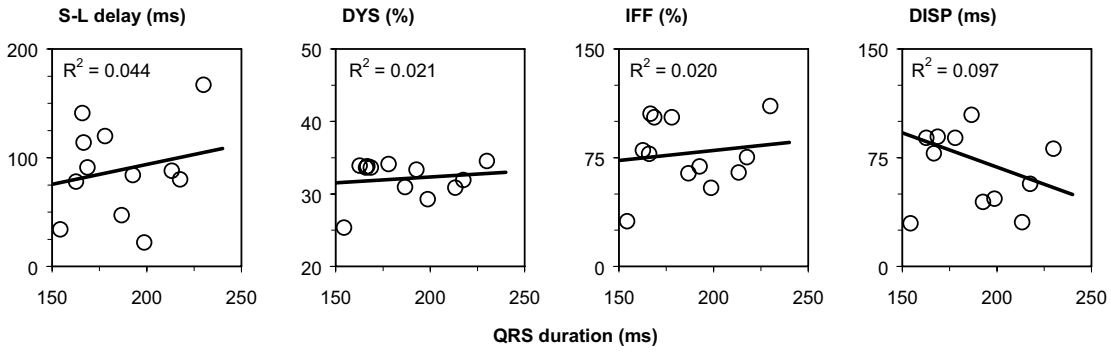


*Figure 5. Linear regression of indices of mechanical dyssynchrony (S-L delay: septal-to-lateral delay of peak systolic velocity obtained by tissue-Doppler echocardiography; DYS: mechanical dyssynchrony; IFF: internal flow fraction; DISP: mechanical dispersion) vs QRS duration as index of electrical 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 indices is technically feasible and should enable immediate quantification of the effects of

interventions and, e.g., 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, cardio-pulmonary interaction and conduction disturbances. Thus, techniques -like MRI- 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 (4ms) is relatively high.

Determination of *absolute* LV volume from the conductance catheter requires careful calibration.[3] In the present study calibration factor parallel conductance was obtained by the hypertonic saline method and slope factor alpha by thermodilution. Slope factor alpha 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±48mL, $p<0.01$). 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 appropriate calibration is performed.[29] As an advantage the dyssynchrony indices 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.[30-32] To test the effects of such underestimations, if present, on our dyssynchrony indices 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.[30,32] The results were compared with the original data using Bland-Altman analysis (Figure 6).[33]

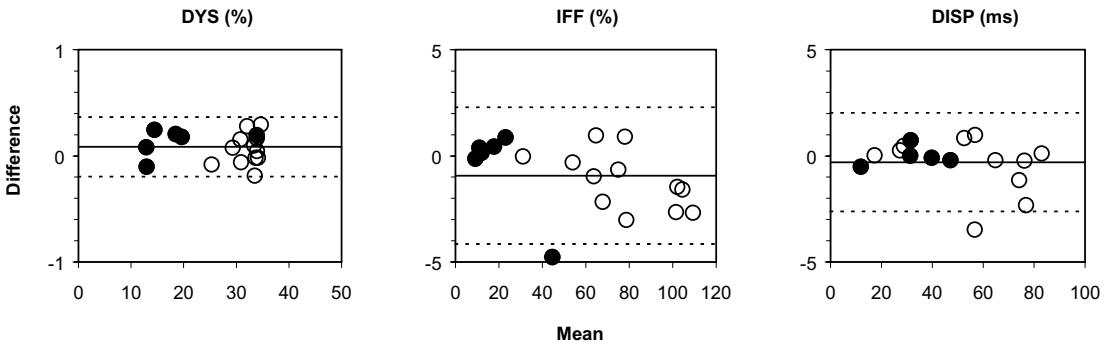


*Figure 6. Bland-Altman analysis comparing conductance catheter derived indices of mechanical dyssynchrony before and after correction of assumed underestimation of segmental volumes due to electric field inhomogeneity. Open circles represent CHF patients, closed circles CAD patients*

The analysis shows no significant bias and fairly narrow limits of agreement for each of the indices indicating that the influence of a potential underestimation of the outer segments on the dyssynchrony indices 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 et al.[34] 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 DISP index. However, Strum et al measured (in degrees) the relative distances between time-points of regional minimal volume and global end-systole, whereas we used the entire systolic wave forms and used cross-correlation to determine the lag-time between segmental and global volume signals. In addition, they compared regional maximal stroke volume with effective stroke volume. The latter was measured using maximums and minimums of the total LV volume as gated markers of the time when regional contraction would contribute to total LV ejection. This effective stroke volume analysis is comparable to our internal flow 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) internal flow. Strum et al 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.[35,36]

**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 and in the catheterization laboratory we used angiography to guide positioning.[37] 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 approximately 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, whereas sternotomy and pericardiotomy are associated with alterations in loading conditions.[38,39,40] Given the anesthesia-related cardiodepression in the CAD patients, one may expect that the differences in the hemodynamic indices 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.[41] Thus we do not expect that the differences in mechanical dyssynchrony between the groups were importantly influenced by the different experimental conditions.

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

Finally, the segmental conductance catheter signals do not provide an anatomical 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 dyssynchrony indices 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 indices quantify various aspects of mechanical dyssynchrony using conductance catheter methodology which, at the same time, can be used for assessment of global systolic and diastolic (dys)function. Diagnostic and prognostic value of the dyssynchrony indices requires further investigation.

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