Cross-Correlation Delay to Quantify Myocardial Dyssynchrony From Phase Contrast Magnetic Resonance (PCMR) Velocity Data

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Abstract

**Purpose**—To apply cross-correlation delay (XCD) analysis to myocardial phase contrast magnetic resonance (PCMR) tissue velocity data and to compare XCD to three established “time-to-peak” dyssynchrony parameters.

**Materials and Methods**—Myocardial tissue velocity was acquired using PCMR in 10 healthy volunteers (negative controls) and 10 heart failure patients who met criteria for cardiac resynchronization therapy (positive controls). All dyssynchrony parameters were computed from PCMR velocity curves. Sensitivity, specificity, and receiver operator curve (ROC) analysis for separating positive and negative controls were computed for each dyssynchrony parameter.

**Results**—XCD had higher sensitivity (90%) and specificity (100%) for discriminating between normal and patient groups than any of the time-to-peak dyssynchrony parameters. ROC analysis showed that XCD was the best parameter for separating the positive and negative control groups.

**Conclusion**—XCD is superior to time-to-peak dyssynchrony parameters for discriminating between subjects with and without dyssynchrony and may aid in the selection of patients for cardiac resynchronization therapy.

Keywords

phase contrast; MRI; myocardial dyssynchrony; cross-correlation; CRT

SPECIFICITY OF PATIENT SELECTION for cardiac resynchronization therapy (CRT) remains poor, as up to 30% of patients selected based on clinically accepted criteria (QRS >120 msec, EF <30%, and New York Heart Association [NYHA] Class III/IV heart failure) do not respond to treatment (1). In addition, sensitivity of patient selection is also less than ideal, as some patients who do not meet these selection criteria may benefit from CRT (2–5).
Mounting evidence suggests that the best way to predict response to CRT is to identify the presence of mechanical dyssynchrony within the left ventricle prior to device implantation (6–11).

Tissue Doppler imaging (TDI) has been used extensively to measure myocardial velocities and quantify mechanical dyssynchrony. While many parameters to quantify dyssynchrony have been proposed, no single methodology has emerged as a widespread standard. Most TDI measurements of dyssynchrony are based on differences in “time-to-peak” systolic myocardial velocity between two or more walls of the left ventricle (LV) (7,12). These time-to-peak methods utilize only a single point from all the data collected over the cardiac cycle and assume that the peak systolic velocity point is the most clinically significant indicator of dyssynchrony. Not only is this a vast underutilization of the acquired data, but the emphasis on peak systolic velocity may reduce accuracy, as these TDI dyssynchrony parameters agree on a diagnosis of dyssynchrony only half the time (13).

A new parameter for quantifying dyssynchrony called cross-correlation delay (XCD) has recently been developed (14). XCD uses a cross-correlation function to calculate a temporal delay between velocity curves in two myocardial regions. Unlike time-to-peak analysis, XCD does not rely on the identification of a single velocity point throughout the cardiac cycle. It has previously been shown that XCD analysis of tissue Doppler velocity data was able to discriminate positive and negative control groups with higher sensitivity and specificity than parameters relying on time-to-peak analysis.

The purpose of the current study was to extend XCD analysis to phase contrast magnetic resonance (PCMR) tissue velocity data. We hypothesize that XCD will have higher sensitivity and specificity for discriminating heart failure patients with dyssynchrony (positive controls) and normal healthy volunteers (negative controls) than parameters of dyssynchrony based on time-to-peak analysis.

**MATERIALS AND METHODS**

**Study Population**

The study population included 10 normal controls (mean age = 36.4 ± 25.1 years, 8 male) and 10 heart failure patients with dyssynchrony (mean age = 63.7 ± 13.4 years, 6 male). Normal controls had no history of cardiac disease, a normal 12-lead electrocardiogram (ECG), and no abnormal findings on cardiac MR. Heart failure patients had ECG evidence of LV dyssynchrony (QRS >150 msec, mean QRS duration = 193.5 ± 28 msec), decreased ejection fraction (EF < 35%, mean EF = 31.9 ± 5.7%), NYHA Class III or IV heart failure, and were being referred for CRT device implantation at our institution. The study was approved by the Institutional Review Board and written informed consent was obtained from all study participants.

**MR Imaging**

MRI exams were performed on a Philips 1.5T Intera CV Magnet (Philips Medial Systems, Best, Netherlands) using a 5-element phased array cardiac coil. Localizer scans were used to determine the position of the myocardium within the chest and cine images were acquired in...
the two-chamber, four-chamber, and short axis orientations. Through-plane (longitudinal) velocity imaging was performed in the short-axis orientation using a segmented, navigator-echo, and ECG-gated sequence (15). The velocity imaging slice was placed at 70% of the total LV length, as measured from the apex to the base in the two-chamber orientation. This basal myocardial location corresponds to where TDI measurements of longitudinal velocity are usually taken. Presaturation slabs were placed on either side of the imaging slice to null the signal from in-flowing blood. Acquisition parameters were as follows: velocity encoding value = 30 cm/s, TR = 7 msec, TE = 4 msec, reconstructed voxel size was 1.4 × 1.4 × 8 mm. Temporal resolution ranged between 26 and 41 msec (18–35 acquired cardiac phases depending on heart rate), with the first cardiac phase acquired 74 msec after the detection of the R-wave due to the leading navigator pulse. Parallel imaging methods to accelerate image acquisition were not used.

Velocity images were imported into MatLab (Math-Works, Natick, MA) for analysis. Endocardial and epicardial borders were manually traced, and the myocardium was segmented according to American Heart Association recommendations (16). This resulted in six myocardial segments from the acquired basal slice (anterior, anteroseptal, inferoseptal, inferior, inferolateral, and anterolateral). Velocity values were spatially averaged in each segment for each timeframe, and a plot of velocity vs. time in the cardiac cycle was generated for each segment.

**Dyssynchrony Measurements**

Four dyssynchrony parameters were computed from the velocity vs. time plots. The septal-to-lateral delay (SLD) was defined as the difference in time-to-peak systolic contraction velocity between the inferoseptal and the anterolateral segments (7). MaxDiff was defined as the maximum difference in time-to-peak systolic contraction velocity between any two of the anterior, inferior, inferoseptal, or anterolateral segments (17). Ts-SD-6 was defined as the standard deviation of time-to-peak in all six basal segments (18).

The cross-correlation delay between two curves was computed by shifting one curve in time relative to the other curve and computing the normalized correlation between the curves for each time shift. The time shift between the two curves that resulted in the maximum correlation value was defined as the temporal delay between the two curves. A temporal delay was computed between the anterior and inferior segments, the anteroseptal and inferolateral segments, and the inferoseptal and anterolateral segments, and the reported XCD was the maximum of these three delays (14). It is important to note that all four dyssynchrony measures (SLD, MaxDiff, TSD-6, and XCD) were computed using the same velocity vs. time plots.

**Statistical Analysis**

Dyssynchrony parameter values for the positive and negative control groups were compared using an unpaired, two-tailed Student’s t-test. To measure the ability of each dyssynchrony parameter to discriminate between the positive and negative control groups, statistical software (SPSS, v. 15.0, Chicago, IL) was used to calculate the area under the receiver operating characteristic (ROC) curves. Areas under the ROC curves were statistically
compared using the method described by Hanley and McNeil (19). *P*-values < 0.05 were considered statistically significant. Threshold values were defined by the point where sensitivity and specificity were equal on the ROC curves.

**RESULTS**

Threshold values for diagnosing dyssynchrony were identified (Fig. 1) for all four dyssynchrony parameters. XCD was the only parameter that was significantly different between the normal and patient groups (mean XCD normals = 10.3 ± 13.3 msec, mean XCD patients = 129.3 ± 114.5 msec, *P* < 0.001). SLD, MaxDiff, and TSD-6 were not significantly different between the two groups (*P* = 0.31, 0.17, and 0.11, respectively). Using the determined threshold values, six normal volunteers had dyssynchrony by SLD criteria, six normals had dyssynchrony according to MaxDiff, and seven normals had dyssynchrony according to Ts-SD-6. In contrast, none of the normal volunteers had dyssynchrony by XCD criteria. Mean values of the four dyssynchrony parameters, as well as the sensitivity and specificity of the determined threshold values, are given in Table 1. Velocity curves and the XCD correlation spectrum from a normal volunteer who had dyssynchrony by all criteria except XCD are shown in Fig. 2. XCD was the only parameter that demonstrated significant discrimination between the normal and patient groups (*P* < 0.001). Area under the ROC curve was 0.38 for SLD, 0.32 for MaxDiff, 0.25 for Ts-SD-6, and 0.93 for XCD (Table 2).

**DISCUSSION**

Our study illustrates that XCD, a dyssynchrony parameter previously developed by Fornwalt et al (14) for the analysis of TDI velocity data, can be extended to the analysis of PCMR velocity data. Four different dyssynchrony parameters (SLD, MaxDiff, Ts-SD-6, and XCD) were computed from PCMR myocardial tissue velocity curves, and XCD was the only dyssynchrony parameter that effectively discriminated between normal volunteers and dyssynchrony patients. An XCD of 31 msec was able to identify dyssynchrony patients with 90% sensitivity and 100% specificity.

The 31-msec threshold reported in our study is consistent with previous findings in echocardiography: an XCD threshold value of 31 msec on TDI velocity data has previously been shown to discriminate between the normal control and patient groups with 100% sensitivity and specificity (14). This study indicates that the same threshold applies to MR velocity curves, despite the fact that the MR curves were acquired at lower temporal resolution than TDI scans.

We computed the sensitivity and specificity of three established dyssynchrony parameters (SLD, MaxDiff, and Ts-SD-6) to separate positive and negative control groups. Sensitivity and specificity of these three dyssynchrony parameters to predict response to CRT have been previously published. SLD >60 msec was found to have a sensitivity of 76% and a specificity of 88% (7), a MaxDiff value >65 msec was shown to separate responders from nonresponders with sensitivity between 78 and 92% and specificity between 33 and 92% (6,20), and Ts-SD-6 >34.5 msec has a reported sensitivity of 70% and a specificity of 92% (21). In the current study, post-CRT follow-up data were not available for our patient group,
so we were unable to quantify the sensitivity and specificity for predicting response to CRT. Instead, in this preliminary study we attempted to discriminate dyssynchrony patients (positive controls) from normal volunteers (negative controls). It was expected that sensitivity and specificity of these parameters for separating normal and patient groups would be higher than for separating responders from nonresponders, but the sensitivities and specificities reported in this study were slightly lower. This may be due to the fact that MR velocity data, not tissue Doppler velocity data, were used to calculate these dyssynchrony parameters.

The PCMR velocity sequence used to acquire myocardial velocity curves has previously been verified to be accurate and reproducible for the acquisition of myocardial velocity data (15), and PCMR myocardial velocities have repeatedly been shown to correlate strongly with myocardial tissue Doppler velocity curves (22,23). Using MRI to assess patients before CRT and assess dyssynchrony has some advantages. In addition to the presence of underlying mechanical dyssynchrony, the response to CRT is also influenced by the presence of myocardial scar at the location of the pacing site and access to the LV pacing site through the coronary veins (24–26). MRI is the only modality that can address all the factors influencing patient response to CRT: PCMR can assess mechanical dyssynchrony, MR delayed contrast enhancement (DCE) imaging can determine the distribution of scar within the LV, and MR coronary venography can determine the coronary venous anatomy (27). While this study did not attempt to address all these factors, it provided the important preliminary step of demonstrating that myocardial PCMR velocity curves can be used to identify the presence of mechanical dyssynchrony.

Cross-correlation analysis has previously been applied to PCMR velocity data to identify areas of infarct based on abnormal wall motion (28). Markl et al (28) identified akinetic myocardial regions by computing the correlation coefficient of velocity within 24 angular LV regions to an average radial velocity curve throughout the entire LV. We applied the same basic principle in this study (cross-correlation analysis), although our analysis focused on identifying the time delay between two myocardial walls rather than deviation from a global myocardial average. Also, Markl et al used radial velocity for their analysis, while our study focused on longitudinal velocity.

Approximately 50% of the normal subjects in this study exhibited dyssynchrony by time-to-peak criteria. While this finding is unexpected, it is consistent with recent results from other studies. The TDI dyssynchrony parameters computed in this study have been shown to agree on a diagnosis of dyssynchrony only half the time (13). Data from the recently released PROSPECT study was unable to identify any TDI measurements that predicted a positive response to CRT (29). Because the XCD parameter considers the entire velocity curve, it is less influenced by single velocity values (such as the fourth point in the inferoseptal region in Fig. 2).

The MR velocity data in this study were acquired at significantly lower temporal resolution than is generally used for TDI studies. However, it is important to realize that the XCD parameter considers all velocity data points acquired throughout the entire cardiac cycle, so
high temporal resolution to accurately identify the timing of peak systolic velocity may not be necessary.

Our study has several limitations. We measured longitudinal (apex-to-base) myocardial velocity in a short axis orientation. Most dyssynchrony measurements are computed on two or four chamber orientations of echocardiographic images. We elected to use the short axis orientation so that we could null the MR signal from inflowing blood and thereby reduce flow artifacts.

Our analysis was conducted using only the longitudinal direction of velocity. Some studies have shown that the circumferential or radial directions may be better at identifying dyssynchrony (30,31), but the vast majority of work has been done with long axis velocities. In the future, we could easily extend our analysis to include these other directions of velocity.

Since velocity data for this study were acquired in a single short axis slice, we were only able to compute the standard deviation of time-to-peak in six basal myocardial segments (Ts-SD-6). It has been shown that Ts-SD-12 (the standard deviation of time-to-peak in 12 basal and midwall segments of the LV) is a more accurate measure of dyssynchrony than Ts-SD-6 (18,32).

Our patient group was carefully chosen to include only those patients with high likelihood of mechanical dyssynchrony (QRS >150 msec, EF <35%) (2,33,34). However, there is no guarantee that all patients in this group truly exhibited mechanical dyssynchrony; this could account for the one patient in our study who had an XCD below the 31-msec threshold.

Finally, the small sample size (10 normal controls, 10 heart failure patients) in our study may have affected our statistical results and caused us to overestimate the utility of the XCD. Additional studies with a greater number of patients are needed in the future.

In conclusion, three dyssynchrony parameters based on time-to-peak analysis (SLD, MaxDiff, and Ts-SD-6) were computed from PCMR longitudinal tissue velocity data and compared to the XCD. XCD was the only parameter that was able to discriminate between normal volunteers (negative controls) and dyssynchrony patients (positive controls). XCD provides a more robust measurement of dyssynchrony than parameters based on time-to-peak analysis and may aid in the selection of patients for CRT.

References


22. Delfino JG, Bhasin M, Cole R, et al. Comparison of myocardial velocities obtained with magnetic resonance phase velocity mapping and tissue Doppler imaging in normal subjects and patients...


Figure 1.
Patient and normal values of the four computed dyssynchrony parameters, as well as the threshold values determined to discriminate between the two groups (threshold shown as the horizontal line). Note that XCD is the only threshold that shows significant separation between normal controls and dyssynchrony patients ($P < 0.05$).
Figure 2.
Longitudinal tissue velocity data from a short axis slice in a normal volunteer. For this subject, SLD = 153 msec, MaxDiff = 178.5 msec, and TSD-6 = 80.2 msec, indicating that the volunteer was considered to have dyssynchrony by all three measurements. In contrast, XCD = 0 msec indicates synchronous myocardial contraction. PCMR velocity data is shown during peak systolic contraction and peak diastolic relaxation. A plot of velocity vs. time in the inferoseptal and anterolateral regions of the myocardium is also shown.
## Table 1

Sensitivity and Specificity of the Four Dyssynchrony Measurements

<table>
<thead>
<tr>
<th>Dyssynchrony parameter</th>
<th>Value in negative control group (msec)</th>
<th>Dyssynchrony threshold (msec)</th>
<th>Negative controls with dyssynchrony</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLD</td>
<td>75 +/-63 msec</td>
<td>74 msec</td>
<td>6</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>MaxDiff</td>
<td>116 +/-80 msec</td>
<td>90 msec</td>
<td>6</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>Ts-SD-6</td>
<td>57 +/-34 msec</td>
<td>47 msec</td>
<td>7</td>
<td>40%</td>
<td>30%</td>
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<tr>
<td>XCD</td>
<td>10 +/-13 msec</td>
<td>31 msec</td>
<td>0</td>
<td>90%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Area under ROC curve</td>
<td>Standard error</td>
<td>Asymptotic significance (P-value for area under ROC curve different from 0.5)</td>
<td>Upper bound of 95% CI</td>
<td>Lower bound of 95% CI</td>
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<tr>
<td>SLD</td>
<td>0.38</td>
<td>0.129</td>
<td>0.364</td>
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<tr>
<td>MaxDiff</td>
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<td>0.129</td>
<td>0.151</td>
<td>0.066</td>
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<tr>
<td>Ts-SD-6</td>
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<td>0.064</td>
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<td>XCD</td>
<td>0.93</td>
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<td>0.001</td>
<td>0.792</td>
<td>1.068</td>
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