Mechanical Dyssynchrony After Myocardial Infarction in Patients With Left Ventricular Dysfunction, Heart Failure, or Both

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**Background**—Mechanical dyssynchrony is considered an independent predictor for adverse cardiovascular outcomes in patients with heart failure. However, its importance as a risk factor after myocardial infarction is not well defined.

**Methods and Results**—We examined the influence of mechanical dyssynchrony on outcome in patients with left ventricular dysfunction, heart failure, or both after myocardial infarction who were enrolled in the Valsartan in Acute Myocardial Infarction (VALIANT) echocardiography study. B-mode speckle tracking with velocity vector imaging was used to assess ventricular synchrony in 381 patients who had image quality sufficient for analysis. Time to regional peak velocity and time to strain rate were measured among 12 left ventricular segments from the apical 4- and 2-chamber views, and the SDs between all 12 segments were used as a measure of dyssynchrony. The relationships between the SD of time to peak velocity and strain rate and clinical outcome of death or heart failure were assessed. In a multivariate Cox model adjusted for clinical and echocardiographic variables, the SD of time to peak velocity (hazard ratio per 10 ms, 1.10; 95% confidence interval, 1.02 to 1.18; \(P=0.010\)) and the SD of time to strain rate (hazard ratio per 10 ms, 1.16; 95% confidence interval, 1.06 to 1.27; \(P=0.001\)) were independent predictors of death or heart failure.

**Conclusion**—Left ventricular dyssynchrony is independently associated with increased risk of death or heart failure after myocardial infarction, suggesting that contractile pattern may play a role in post–myocardial infarction prognosis.

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**Key Words:** echocardiography ■ heart failure ■ myocardial infarction

Left ventricular dyssynchrony has a deleterious effect on hemodynamic function and prognosis in patients with heart failure.1–3 In addition, correction of dyssynchrony with cardiac resynchronization therapy has been shown to improve immediate hemodynamics, symptoms, quality of life, exercise tolerance, and survival in patients with heart failure.4–7

**Clinical Perspective on p 1103**

Although asynchronous motion is often apparent in patients with myocardial infarction (MI) and has been associated with infarct size6 and left ventricular remodeling at 6 months,9 the relationship between ventricular synchrony and prognosis after MI remains unclear. We used data from the Valsartan in Acute Myocardial Infarction (VALIANT) study to test the hypothesis that left ventricular dyssynchrony would affect clinical outcome after acute MI.

**Patient Population**

Six hundred ten patients from the main VALIANT population were enrolled in the VALIANT echocardiography study10,11 between 12 hours and 10 days (mean, 4.8 days) after the onset of acute MI. All enrolled patients had left ventricular dysfunction (ejection fraction <35% on echocardiography or ventriculography or ejection fraction <40% on radionuclide imaging), clinical evidence of heart failure at the time of presentation, or both. A total of 381 patients had image quality sufficient for analyzing dyssynchrony based on B-mode speckle tracking methods. We excluded 222 patients from analysis because of insufficient 2-dimensional image quality, which included out-of-plane images and endocardial dropout, and 7 patients because baseline data were insufficient or missing. Patients were followed up 6 times during the first year and every 4 months thereafter. All prespecified end points were adjudicated by a clinical end-point committee. Hospitalization for heart failure was

**Methods**

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Guest Editor for this article was James D. Thomas, MD. Our trial (VALIANT) was performed before trial registration was required. Correspondence to Scott D. Solomon, MD, Cardiovascular Division, Brigham and Women’s Hospital, 75 Francis St, Boston, MA 02115. E-mail ssolomon@rics.bwh.harvard.edu

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defined as unplanned intravenous treatment of new or worsening heart failure with inotropic agents, diuretics, or vasodilators requiring overnight stay in or admission to any healthcare facility after the index infarction; cardiovascular mortality was defined as sudden death or death attributed to recurrent MI, heart failure, a cardiovascular procedure, stroke, or other cardiovascular cause.10

**Echocardiographic Analysis**

Echocardiographic images on videotape were digitized and converted to DICOM digital images with a frame rate of 30 Hz. Standard echocardiographic parameters, including ventricular volumes and ejection fractions, were analyzed with an offline analysis workstation as previously described.11–14 Dyssynchrony indexes were measured with B-mode speckle tracking software (velocity vector imaging, Axius VVI 2.0, Siemens Medical Solutions, Malvern, Pa) that circumvents angle dependency and identifies cardiac motion by tracking multiple reference points, inward and outward border motion, motion of tissue along the direction of the border, and periodicity between cardiac cycles.15–19 After tracing the subendocardium of the left ventricle, the semiautomated tracking algorithm outlined the myocardium from frame to frame throughout the cardiac cycle, and velocity vectors, overlaid onto the B-mode image, were displayed with the direction and relative speed of the tissue. Tracking quality was verified for each segment with manual adjustment if necessary. The software automatically divided the apical images into 6 standard segments and provided velocity vector profiles of myocardial motion. Longitudinal velocity and strain-rate curves were derived from each basal, mid, and apical segment in apical 4- and 2-chamber views (Figure 1). Time to regional peak velocity (Tvel) or strain rate (Tsr) was measured during the ejection phase, and the SDs between all 12 segments were used as a measure of dyssynchrony.10,14 The higher peak was selected when the double peaks were encountered, and the segment was excluded from calculation of these dyssynchrony indexes if a positive velocity or a negative strain rate was not observed during systole (2% of all segments from 53 patients).

**Comparison of Strain and Time With Peak Strain Measures Between Videotapes and Digital Images**

To assess the validity of data obtained from videotapes, we performed a validation study using echocardiographic images from 30 separate patients with optimal image quality. Images were stored in the DICOM digital format directly on the ultrasound machines and transferred to a computer workstation with a frame rate of 30 Hz for offline analysis. Those same images were simultaneously recorded on videotape and were subsequently digitized and converted to DICOM digital images. Peak strain rate and Tsr from apical views were measured and compared using velocity vector imaging in the same manner as described above. To test the effect of frame rate on measurements, 20 studies were recorded at both higher frame rates (mean, 72 frames per second; range, 56 to 82 frames per second) and lower frame rates (30 frames per second) and were also compared.

Statistical Analysis

Summary information for continuous variables was expressed as mean±SD and for categorical variables as counts and percents. We categorized the patients in tertiles according to the strain rate–based dyssynchrony index and applied Wilcoxon rank-sum tests for trend across ordered groups. Cox proportional-hazards regression models were used to assess the independent value of dyssynchrony indexes after we verified that the proportional-hazard assumption was met graphically. The adjustment model included the 10 most powerful predictors of mortality, which were identified from the overall VALIANT study using stepwise elimination and backward selection of a 70-covariate model (age, history of diabetes mellitus, history of heart failure, prior MI, history of chronic obstructive pulmonary disease, percutaneous transluminal coronary angioplasty after MI, history of angina after MI, atrial fibrillation complicating MI, Killip class, and estimated glomerular filtration rate) plus left ventricular ejection fraction.11,22 Event curves for the composite outcome of mortality or heart failure were derived from Kaplan–Meier survival analysis with the log-rank test for statistical significance. For each Cox regression model with Tvel-SD and Tsr-SD, the predictive performance was evaluated with the C statistic using the Pencina and D’Agostino23 method, and statistical comparisons between 2 C statistics were also performed by bootstrapping 1000 times using random resampling by replacement.24

Linear regression and correlation analysis were used to compare the data obtained from video-derived digitized images and DICOM-based digital images obtained directly on the ultrasound machines and to compare the measurements between the images at high frame rates and low frame rates. Bland-Altman analysis was performed to compute the bias and 95% limits of agreement. The intraobserver and interobserver variabilities were assessed in 35 randomly selected patients. The coefficients of variability were 7.1% and 8.2% for...
strain rate and 12.8% and 13.9% for Tsr, respectively. For all tests, a value of \( P < 0.05 \) was considered significant.

All authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**Comparison of Strain and Time With Peak Strain Measures Between Videotapes and Digital Images**

We compared simultaneously acquired digital and video-recorded data from 30 separate patients in a validation analysis. Comparison of measures of peak strain rate and Tsr from each individual segment is shown in Figure 2, top (left, segmental strain rate: \( r = 0.61, P < 0.005 \); right, segmental Tsr: \( r = 0.52, P < 0.005 \)). Global strain rate and the SD of Tsr from videotapes compared with those measurements from digital data obtained directly on the machines demonstrated good correlation between global digital and video measures (Figure 2B, left; global strain rate: \( r = 0.87, P < 0.005 \); right, Tsr-SD: \( r = 0.83, P < 0.005 \)). Bland-Altman analysis revealed a bias of 0.04 (95% limits of agreement, \(-0.13 \) to \(0.21\)) for strain rate

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**Figure 2.** Correlation plots of segmental systolic strain rate and time to peak systolic strain rate between digital images and videotapes (A), of global systolic strain rate and the SD of time to peak systolic strain rate between digital images and videotapes (B), and between the images at high and low frame rates (C).
and −1.51 (95% limits of agreement, −11.49 to 14.50) for Tsr-SD. Likewise, good correlation was also observed between the strain rate and Tsr-SD at low and high frame rates (Figure 2C). Whereas a tendency to underestimate the peak strain rate appeared at the low frame rates, the SD of timing Tsr-SD. Likewise, good correlation was also observed between the strain rate and Tsr-SD at low and high frame rates (Figure 2C). Whereas a tendency to underestimate the peak strain rate appeared at the low frame rates, the SD of timing

Baseline Characteristics

Baseline characteristics of the patients included in the dysynchrony analysis were comparable to the remainder of the VALIANT echocardiography cohort with respect to age, gender, Killip class, history of diabetes mellitus, dyslipidemia, prior MI, thrombolytic therapy, primary percutaneous angioplasty, estimated glomerular filtration rate, and medication. The dysynchrony cohort had a lower body mass index (27.2 versus 29.4 kg/m²; P<0.001), a lower rate of hypertension (52.2% versus 63.0%; P=0.01), and a prior history of heart failure (13.1% versus 20.1%; P=0.04).

Predictors for Clinical Events and Mortality

During follow-up (median, 611 days), a total of 67 patients (17.5%) died, 61 (15.9%) as a result of a cardiovascular cause, and 105 patients (27.4%) died of or were hospitalized for heart failure. The Kaplan–Meier estimate of the time to death from any cause or hospitalization for heart failure was significantly increased and left ventricular ejection fraction; LV, mitral early diastolic velocity; A, mitral late diastolic velocity; DT, deceleration time; MR, mitral regurgitation; and LA, left atrial. All values are given as mean±SD unless otherwise indicated. *P<0.05.

Table 1. Demographic and Clinical Characteristics of Patients According to the Degree of Dyssynchrony

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Tsr-SD &lt;44 ms (n=127)</th>
<th>Tsr-SD ≥44 ms (n=127)</th>
<th>Tsr-SD ≥63 ms (n=127)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>96 (75.6)</td>
<td>84 (66.1)</td>
<td>89 (70.1)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Table 2. Echocardiographic Characteristics of Patients According to the Degree of Dyssynchrony

<table>
<thead>
<tr>
<th>LVESV indexed, mL/m²</th>
<th>Tsr-SD &lt;44 ms (n=127)</th>
<th>Tsr-SD ≥44 ms (n=127)</th>
<th>Tsr-SD ≥63 ms (n=127)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>32.9±7.7</td>
<td>36.5±11.1</td>
<td>43.9±14.4</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
</tbody>
</table>

Dyssynchrony severity at baseline was associated with older age, hypertension, history of MI, heart failure, and longer QRS duration and inversely related to percutaneous coronary angioplasty (Table 1). In addition, left ventricular end-diastolic and end-systolic volumes, left ventricular mass index, left atrial volume, infarct length, and mitral regurgitation were significantly increased and left ventricular ejection fraction was reduced in patients with severe dyssynchrony at baseline (Table 2). Higher wall motion score was associated with prolonged Tsr (P<0.005).
nary angioplasty after MI, atrial fibrillation complicating MI, Killip class, estimated glomerular filtration rate, and ejection fraction (adjusted hazard ratio, 1.88; 95% CI, 1.10 to 3.23; \( P = 0.021 \) for Tvel-SD; adjusted hazard ratio, 2.49; 95% CI, 1.40 to 4.44; \( P = 0.002 \) for Tsr-SD).

The hazard ratios associated with each 10-ms increase in the dyssynchrony index for each of the assessed outcomes are shown in Table 3. In a multivariate model, the dyssynchrony index was independently predictive of the combined end points of death or heart failure (Tvel-SD, \( P = 0.010 \); Tsr-SD, \( P = 0.001 \)). Dyssynchrony index remained an independent predictor of outcome even when wall motion score was substituted for ejection fraction (adjusted hazard ratio 1.09; 95% CI, 1.01 to 1.17; \( P = 0.021 \) for Tvel-SD per 10 ms; adjusted hazard ratio, 1.12; 95% CI, 1.02 to 1.23; \( P = 0.023 \) for Tsr-SD per 10 ms). There was no significant difference between Tvel-SD and Tsr-SD for predicting clinical outcomes (C statistic, 0.74; 95% CI, 0.69 to 0.78 for Tvel-SD; C statistic, 0.74; 95% CI, 0.70 to 0.79 for Tsr-SD; \( P = 0.42 \)), whereas concordance was fair between Tvel-SD and Tsr-SD relative to the tertile classification (\( \kappa = 0.30 \)).

### Discussion

Our data show that in patients with high-risk MI, ventricular dyssynchrony was an independent predictor of death or heart failure even after adjustment for clinical and echocardiographic covariates. These results suggest that ventricular contraction pattern may be an important determinant of prognosis independently of overall ventricular function or regional wall motion abnormalities.

Although frank bundle-branch block has been associated with unfavorable prognosis in patients with acute MI, we have previously shown that prolonged QRS duration, even

#### Table 3. Estimated Hazard Ratios for Overall Outcomes According to Dyssynchrony Indexes

<table>
<thead>
<tr>
<th>Hazard Ratio* (95% CI)</th>
<th>Death or Hospitalization for HF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All-Cause Mortality</td>
</tr>
<tr>
<td>Event, n</td>
<td>67/381</td>
</tr>
<tr>
<td>Tvel-SD/10 ms</td>
<td>1.10 (1.01–1.20)*</td>
</tr>
<tr>
<td>( P )</td>
<td>( &lt;0.001 )</td>
</tr>
<tr>
<td>Tsr-SD/10 ms</td>
<td>1.18 (1.08–1.30)*</td>
</tr>
<tr>
<td>( P )</td>
<td>( &lt;0.001 )</td>
</tr>
<tr>
<td>Tvel-SD/10 ms</td>
<td>1.03 (0.94–1.13)†</td>
</tr>
<tr>
<td>( P )</td>
<td>0.54</td>
</tr>
<tr>
<td>Tsr-SD/10 ms</td>
<td>1.10 (0.98–1.23)†</td>
</tr>
<tr>
<td>( P )</td>
<td>0.11</td>
</tr>
</tbody>
</table>

*Unadjusted.
†Adjusted for age, history of diabetes mellitus, history of heart failure, history of prior MI, history of angina before MI, history of chronic obstructive pulmonary disease, percutaneous coronary angioplasty after MI, atrial fibrillation complicating MI, Killip class, estimated glomerular filtration rate, and left ventricular ejection fraction.
within the normal range, was associated with adverse outcome in patients with high-risk MI.\textsuperscript{14} Although QRS width is clearly related to mechanical dyssynchrony, significant mechanical dyssynchrony could be present even in the absence of substantially increased QRS duration.\textsuperscript{2,3} In our data set, only a few patients showed abnormal electric activation, and 7% of the patients with the highest tertile of dyssynchrony had wide QRS $\geq$120 ms, suggesting that the dyssynchrony observed in the post-MI setting might more likely be a result of the MI itself rather than abnormalities of the conduction system. The finding in the present analysis that mechanical dyssynchrony was predictive of outcome independently of global or regional contractile function suggests that this measure was not simply a surrogate for global or regional wall motion, known to be strongly related to outcome after MI.\textsuperscript{13,25}

Our data suggest that ventricular dyssynchrony may contribute to adverse prognosis and development of heart failure in the post-MI setting and demonstrate a pathophysiological link between ventricular activation and outcome in the post-MI patient that is independent of measures of ventricular function. Mechanical dyssynchrony is recognized as an independent predictor of adverse clinical events and worse survival in patients with heart failure,\textsuperscript{1–3} and cardiac resynchronization therapy has been shown to benefit some heart failure patients with improvement of clinical symptoms and outcomes.\textsuperscript{4–7} Experimental and clinical reports have demonstrated that dyssynchrony results in decreased cardiac output, slowed relaxation rates, and reduced peak filling velocity, as well as increased myocardial energy demand.\textsuperscript{26–28} Furthermore, asynchronous contraction itself may result in redistribution of myocardial fiber strain and blood flow\textsuperscript{29,30} and may be associated with abnormalities of myocardial perfusion.\textsuperscript{31,32} Abnormal patterns of contraction and myocardial stretch are likely to increase mechanical loading and myocardial work and potentially could impair functional recovery after ischemic injury.\textsuperscript{33} Mollema et al\textsuperscript{9} have demonstrated that ventricular dyssynchrony immediately after MI was associated with increased ventricular remodeling at a 6-month follow-up. However, the relationship between dyssynchrony and post-MI remodeling might be more complicated, depending on the period and duration. Indeed, Vanagt et al\textsuperscript{34,35} have shown that pacing-induced intermittent dyssynchrony before ischemia or during early perfusion may modulate myocardial workload and thus could be protective through preconditioning and postconditioning.\textsuperscript{34,35} The increased dyssynchrony associated with greater mitral regurgitation suggested by these data suggests another potential mechanism by which dyssynchrony might be related to outcome. Mitral regurgitation after MI is usually secondary to alternations in myocardial structure and function rather than due to abnormalities of the mitral leaflets themselves, is known to be associated with worse outcomes after MI, and thus might contribute to the adverse effects of worsened ventricular synchrony.\textsuperscript{12,36}

Two-dimensional speckle tracking has enhanced the ability to assess regional and global myocardial properties noninvasively because of its angle independence, which overcomes the limitations of tissue Doppler imaging.\textsuperscript{37,38} The specific method used in this analysis, velocity vector imaging,\textsuperscript{15–19} has been recently validated with sonomicrometry.\textsuperscript{17} Moreover, these methods allow retrospective analysis of echocardiographic images obtained under standard conditions and do not require collection of raw data. Our own validation of these techniques comparing video recorded and digital data suggests that these methods could potentially be used in a wide variety of equipment and therefore could be applied to a rich set of available clinical data. We found that analyses of Tvel or Tsr were not significantly different with respect to predictive value, although Tsr has some potential advantages in that it measures the timing of true myocardial contractile motion rather than simply passive myocardial motion, which could be substantial in the post-MI setting. Recently published data have suggested the superiority of strain-based measures of dyssynchrony to velocity-based measures in predicting responses to biventricular pacing.\textsuperscript{39–41} Nevertheless, it should be noted that these methods are cumbersome and are not recommended as a method to assess synchrony but were used in this analysis as a tool to understand the pathophysiological link between synchrony and outcome independently of global or regional systolic function.

Some limitations of our analysis should be noted. Dyssynchrony assessment with this technique was not possible in 37% of our cohort because of insufficient image quality. Although B-mode–based speckle tracking techniques may be more robust than Doppler-based methods to assess strain, a number of factors can reduce data quality, including lateral resolution in the far field, out-of-plane motion, and image dropout. Videotape processing further downgrades image resolution, potentially introducing anisotropy and limiting the utility of the technique. This methodology was used for analysis of VALIANT data simply because digital data were not available and VALIANT represents a very well-characterized high-risk post-MI data set with well-characterized outcomes data. Although our own analyses suggest the relative comparability of these techniques to direct digital analyses for the purposes described here, we do not advocate this methodology when fully digital data are available. Although our validation data suggest that the temporal resolution and lower frame rate of videotape may also marginally reduce the robustness of the data, prior studies have shown that this frame rate is feasible for acquiring velocity and strain curve for time parameters, and all of these limitations would tend to attenuate the relationship between these measures and outcomes.\textsuperscript{16,18,42} Although it is possible that our multivariable model may not have accounted for all confounders, we used the 10 most robust confounders identified in the overall VALIANT data set to avoid overfitting in the models. Finally, although resynchronization therapy has been shown to benefit patients with heart failure and left ventricular dysfunction, the greatest benefit has been observed in patients with nonischemic left ventricular dysfunction.\textsuperscript{4–6} and our data provide no direct evidence that resynchronization therapy would benefit patients in the post-MI setting.

**Conclusions**

In patients with left ventricular dysfunction, heart failure, or both, mechanical dyssynchrony was an independent predictor of outcome after MI. These results suggest that contractile
pattern may be an important determinant of the development of heart failure after MI independently of global and regional contractile function.

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