Quantification of Left Ventricular Function With Premature Ventricular Complexes Reveals Variable Hemodynamics

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Background—Premature ventricular complexes (PVCs) are prevalent in the general population and are sometimes associated with reduced ventricular function. Current echocardiographic and cardiovascular magnetic resonance imaging techniques do not adequately address the effect of PVCs on left ventricular function.

Methods and Results—Fifteen subjects with a history of frequent PVCs undergoing cardiovascular magnetic resonance imaging had real-time slice volume quantification performed using a 2-dimensional (2D) real-time cardiovascular magnetic resonance imaging technique. Synchronization of 2D real-time imaging with patient ECG allowed for different beats to be categorized by the loading beat RR duration and beat RR duration. For each beat type, global volumes were quantified via summation over all slices covering the entire ventricle. Different patterns of ectopy, including isolated PVCs, bigeminy, trigeminy, and interpolated PVCs, were observed. Global functional measurement of the different beat types based on timing demonstrated differences in preload, stroke volume, and ejection fraction. An average of hemodynamic function was quantified for each subject depending on the frequency of each observed beat type.

Conclusions—Application of real-time cardiovascular magnetic resonance imaging in patients with PVCs revealed differential contribution of PVCs to hemodynamics. (Circ Arrhythm Electrophysiol. 2016;9:e003520. DOI: 10.1161/CIRCEP.115.003520)

Key Words: cardiac arrhythmias | echocardiography | magnetic resonance imaging | stroke volume | ventricular premature complexes
WHAT IS KNOWN

- Idiopathic premature ventricular complexes (PVCs) may create variable symptoms and are thought to cause a cardiomyopathy. Clinically, PVC-induced cardiomyopathy remains a diagnosis of exclusion.
- Conventional imaging is often used to rule out underlying disease. Techniques, such as conventional multishot MRI and echocardiography, do not provide information on the hemodynamic function of different beat types.

WHAT THE STUDY ADDS

- Single-shot 2-dimensional magnetic resonance imaging, when synchronized with ECG recording, can yield volumetric information on different beat types in patients with PVCs.
- The technique demonstrates that patients with similar prevalence of PVC can have different hemodynamic functions because of the stroke volume of each beat type and the relative prevalence. This approach opens the door for more detailed evaluation of patients with suspected PVC-induced cardiomyopathy.

which allows for identification of different beat types based on RR intervals and the measurement of global LV volume via summation of 2D slice data covering the entire heart for each beat type.

Image Reconstruction and Slice Volume Quantification

The real-time image reconstruction and slice volume quantification methods have recently been validated in animals and in clinical patients. Briefly, image reconstruction was performed using a non-Cartesian parallel imaging (SENSE-based) algorithm in open-source software with 34 radial projections per image (image exposure time, 95.2 ms) and maximal view sharing (frame rate, 357 fps). Quantification of real-time images was performed through user-initialized active contour segmentation, which has been shown to provide slice volume values comparable with manual segmentation using clinical tools. Papillary muscles were excluded from the segmentation using the feature image and manual correction. The basal slice was determined by identification of the slice with mitral valve annular plane at end systole. LV slice volume was quantified from segmented data using the pixel size and slice thickness.

ECG Recording and Synchronization

ECGs recorded in a magnetic field are distorted by the magnetohemodynamic effect, which limits the interpretability of the 3-lead ECG when compared with a 12-lead ECG outside of the magnet. However, because of the need for ECG gating in cine CMR, robust 3-lead (ECG) acquisition, filtering, and real-time display are standard features of clinical CMR scanners. For this work, we implemented a logging algorithm to capture the ECG signal acquired during CMR. This results in synchronization between the ECG signal, real-time CMR image frames, and derived slice volume quantification as shown in Figure 1. The ECG distortion did not hinder the detection of QRS peaks and allowed for quantification of RR durations. Although QRS morphology is distorted by the magnetic field, the distortion is consistent across the same PVC beat type, which allowed for identification of each PVC beat type in all patients and exclusion of premature atrial contractions. ECG recording was continuous and synchronous during the imaging of the entire short axis of the LV. PVC burden was quantified as the percentage of total beats during the scanning session.

Categorization of Beats

After detection of the R wave of the QRS complex via Pan–Tompkins algorithm implemented in Matlab (Mathworks, Natick MA), different beats were identified and categorized based on 2 measured RR

Figure 1. Two-dimensional real-time cardiovascular magnetic resonance imaging with synchronized ECG recording and measurement of slice volume over time. Top, A projection through the heart where the contraction of the left ventricle begins in sinus rhythm and transitions to premature ventricular complexes (PVCs). Middle, Synchronously recorded ECG with the identification of the R wave demarcated by a red triangle for sinus beats and green triangle for PVC beats. Bottom, Quantification of slice volume allows for observation of the change in slice function because of arrhythmia. The slice volume associated with the R wave (beginning of contraction) is shown via dots. For sinus contractions, the red dots occur close to the maximum slice volume (left ventricular end-diastolic volume [LV EDV]). However, during a PVC, the green dots indicate PVC preload, which may be substantially lower than the LV EDV.
Figure 2. Two-dimensional (2D) RR duration plot. Grouping of beat types based on beat duration RR_{i} and loading (previous) beat duration RR_{i-1}. Left, A patient with sinus rhythm is shown with a single ECG and 1 2D cluster. Middle, A patient with a single premature ventricular complex (PVC) (green triangle) demonstrates how the algorithm can be used to provide arrhythmia rejection. When PVCs are infrequent, they are not observed at all slice locations and therefore did not result in global volume measurements. Right, A patient in trigeminy exhibits 4 beat clusters. Three clusters (with colored boxes) were observed at all slice locations. The remaining cluster (sinus–sinus) was only observed at a single-slice location and is, therefore, excluded from further analysis.

Global Volume Estimation

For each beat type, global volume estimates were obtained by summation of slice volumes obtained across the LV (Figure 3). To account for small variations in RR duration, nonlinear beat duration normalization was performed before summation.12 Global volume over time was obtained only in beat types that were observed at all LV slice locations.

Global volume estimates made during PVCs are illustrated in Figure 4. Subject 6 has a regular bigeminy pattern (Figure 4A), and 2 beat types (clusters) are identified in Figure 4B. Figure 4C and 4D illustrate the close agreement in ECG morphology across the observed beats. The global volume over time for each beat type is obtained by summation of slice volumes over time.

Quantification of Beat-by-Beat Function

Global maximum volume (V_{max}) (end-diastolic volume in sinus beats and loading volume in PVC beats), global minimum volume (V_{min}) (end-systolic volume in sinus beats and smallest volume in the PVC beats), stroke volume (SV; V_{max}−V_{min} for the beat), and ejection fraction (EF; SV/V_{max}) were obtained for each observed beat type. The prevalence of each type was used to obtain a temporally averaged estimate of function. The prevalence of each beat type was calculated as the percentage of beats identified in that beat type relative to the number of beats used for global volume estimation of all beat types. LVEF obtained from clinically performed echocardiography examinations were compared with magnetic resonance imaging–derived values when available.

Evaluation of PVC Function Across Subjects

To understand the relationship of PVC timing with SV produced by the PVCs, we plotted the SV of PVC contractions (normalized to the SV observed in sinus or interrupted sinus beats in that subject) versus loading duration of the PVC (normalized by the loading duration of sinus beats in the same subject). SV/V_{max} was used for normalization.

Intraobserver and Interobserver Variability

The variation in the proposed approach stems mainly from the reproducibility of semiautomated segmentation of the individual LV slices.
To quantify this variability, a midventricular slice was resegmented by the same observer and by a second observer for each imaging study (n=17). The slice end-diastolic volume and end-systolic volume were estimated from 5 consecutive heartbeats as the mean maximum and mean minimum slice volume, respectively.

Statistical Analysis
Nonparametric Wilcoxon signed-rank test (P<0.05) was used to detect significant differences in the comparison of PVC burden between patients with normal and abnormal LVEF and differences between echo- and magnetic resonance imaging–derived EF. Skewness and kurtosis tests for normality were performed for SV and EF after normalizing the volumes to each subject’s sinus or interrupted sinus beat. Repeated measures ANOVA were performed to evaluate differences in SV and EF among different beat types (sinus, interrupted sinus, post-PVC sinus, and PVC). Intraobserver and interobserver reliability was quantified by coefficient of variation and Pearson correlation coefficient. Statistical analyses were performed using Stata 13 (StataCorp, College Station, TX).

Results
Sinus Rhythm and Low Frequency of PVCs
In 5 subjects (Table 1, patients 1–4 and 5 post ablation), only 1 beat type (sinus rhythm) was observed across all slice locations, and thus, 1 mode of ventricular volume and function was quantified (Figure 3). These subjects were in sinus rhythm despite having a history of frequent PVCs (patients 1 and 2) or had infrequent PVCs (4%, 7%, and 8% PVC burden [patients 3, 4, and 5 post ablation]) during the imaging session. These PVCs were not observed at all slice positions and could not be quantified with data obtained during the scanning session.

High Frequency of PVCs in Different Ectopic Patterns
The remaining 10 subjects had PVCs that were observed in all slice locations during imaging (13%–50%). The PVC burden calculated based on the ECG differs from that prevalence of beat types because of changes in rhythms (eg, sinus to trigeminy or bigeminy to trigeminy). As a result, the beat types described in Table 1 may not contain all of the cardiac contractions; hence, the sum of beat frequencies is <100%.

Subject 6 was imaged twice and was in regular bigeminy during the first real-time CMR. As a result, 2 beat types were observed (Figure 4). The lower EF of the PVC was a result of less effective contraction with similar loading volume as the post-PVC sinus contraction, leading to a higher $V_{min}$. During the second imaging session, the same subject had frequent PVCs (40%) without a regular pattern. The PVCs were less effective toward cardiac output than the PVCs in bigeminy and contributed half of the SV compared with sinus beats (23.5 versus 52.9 mL). Despite the difference in ectopic patterns at different time points, the temporally averaged EFs were similar (48.7% versus 50.1%) during the 2 imaging sessions.

Subject 7 was in regular trigeminy during the real-time CMR, which resulted in 3 beat clusters (Figure 5). In addition to the PVC, the 2D RR-duration plot allowed for the interrupted sinus cluster to be quantified separately from the post-PVC sinus and sinus–sinus cluster as shown in Figure 5C and 5D. $V_{min}$ associated with the post-PVC sinus was smaller than the interrupted sinus (38.7 versus 65.8 mL), which resulted in a higher calculated EF (69.5% versus 50.5%). The PVCs (Figure 5E) in this pattern had a small SV (9.6 mL). As a result, this patient demonstrated 2 contractions (interrupted sinus and post-PVC sinus) that produced high SVs and 1 contraction (PVC) that produced low SV.

Subject 8 had interpolated PVCs during the image acquisition (Figure 6), which resulted in a unique pattern not described above. Interpolated PVCs are PVCs that occur in between sinus depolarizations without compensatory pause after the PVC. In this case, there are 2 short RR intervals...
Table 1. Beat Characteristics, Volumetric Measures, and Weighted Average of Study Subjects

<table>
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<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Sex</th>
<th>Arrhythmia Type</th>
<th>PVC Prevalence, %</th>
<th>Beat Type</th>
<th>Loading Beat Duration, ms</th>
<th>Beat Observations</th>
<th>Volumetric Measures</th>
<th>Beat Frequency, %</th>
<th>Temporal Average EF, %</th>
<th>Echo-Derived EF, %</th>
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The loading volume for the post-PVC sinus contraction (94.4 mL) decreased relative to normal sinus beats (126.8 mL). The post-PVC contraction resulted in a decrease in EF (34.6% versus 42.6%). Furthermore, the PVC did not result in substantial SV (14.0 mL). As a result, interpolated PVCs resulted in a decreased SV not only in the PVC beat but also in the post-PVC beats.

Subjects 9 to 15 and subject 5 prior to ablation had a variety of patterns, including periods of bigeminy and trigeminy, as well as PVCs late in diastole. The different arrhythmia patterns resulted in different numbers of beat types being observed, which are also shown in Table 1.

After normalizing the SV and EF to each subject’s sinus or interrupted sinus beats, both variables were tested and found to be normally distributed. There were statistically significant differences in SV (P<0.0001) and EF (P<0.0001) between PVC and non-PVC beats. Differences between non-PVC beats (sinus, interrupted sinus, and post-PVC sinus) were not significant (SV, P=0.30; EF, P=0.51).

In 5 subjects, clinical echocardiograms were performed prior to CMR examination. The echo-derived EF was assessed using the biplane method and is shown in Table 1. When compared with non-PVC contractions from real-time CMR, the values show close agreement (P=0.84; R²=0.986; coefficient of variation=5.8%).

### Table 1. Continued

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<th>Patient No.</th>
<th>Age</th>
<th>Sex</th>
<th>Arrhythmia Type</th>
<th>PVC Prevalence, %</th>
<th>Beat Type</th>
<th>Loading Beat Duration, ms</th>
<th>Beat Observations</th>
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<th>SV, mL</th>
<th>EF, %</th>
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<td>35.1</td>
<td>47.7</td>
<td>14</td>
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<tr>
<td>14</td>
<td>90</td>
<td>M</td>
<td>PVC</td>
<td>14</td>
<td>Post PVC/ sinus</td>
<td>1106.2</td>
<td>14</td>
<td>126.6</td>
<td>65.1</td>
<td>51.4</td>
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<td>52</td>
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<td>Interrupted sinus</td>
<td>936.9</td>
<td>98</td>
<td>127.1</td>
<td>65.5</td>
<td>51.5</td>
<td>9</td>
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<td></td>
<td>PVC</td>
<td>565.6</td>
<td>19</td>
<td>66.9</td>
<td>7.8</td>
<td>11.6</td>
<td>9</td>
<td>...</td>
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<tr>
<td>15</td>
<td>27</td>
<td>F</td>
<td>PVC</td>
<td>13</td>
<td>Post PVC/ sinus</td>
<td>1292.5</td>
<td>18</td>
<td>87.2</td>
<td>49.0</td>
<td>56.2</td>
<td>64</td>
<td>50.8±14.5</td>
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<td></td>
<td></td>
<td>Interrupted sinus</td>
<td>977.7</td>
<td>207</td>
<td>99.2</td>
<td>57.5</td>
<td>58.0</td>
<td>12</td>
<td>...</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PVC</td>
<td>599.8</td>
<td>130</td>
<td>63.2</td>
<td>8.7</td>
<td>13.8</td>
<td>12</td>
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</table>

EF indicates ejection fraction; F, female; M, male; PVC, premature ventricular complexes; and SV, stroke volume.

### PVC SV and Timing
To further understand the relationship of PVC timing with SV produced by the PVCs, we plotted the SV of the PVC (normalized to the SV observed during sinus contractions in that subject) versus loading duration of PVC (normalized by the loading duration of sinus beats in the same subject) as shown in Figure 7. The SV of PVC correlated poorly to the timing in the cardiac cycle (linear fit: slope=0.27; y intercept=23.6; R²=0.03; P=0.552).

### Interobserver and Intraobserver Reproducibility
The reproducibility results are shown in Table 2. Pearson coefficient values were high for both cardiac phases and intraobserver and interobserver measurements.

### Discussion
In this work, we have demonstrated a technique, which combines a 2D real-time magnetic resonance imaging technique and simultaneous ECG logging to quantify ventricular volumes. This technique allowed us to characterize different PVCs by volume and compare them with other beats in the same subject, which revealed differential SV and contribution to cardiac output. In subjects with similar PVC frequencies, the hemodynamic effect of PVCs occurring in different patterns can be significantly different. In addition, we have
reported that PVCs can potentially lower subsequent sinus loading volume rather than augmenting it.

Assessment of LV Function

There is currently no standard noninvasive method to assess the volumes and functions of PVCs in addition to sinus contractions. In echocardiography, which has been used as the standard in evaluating patients with suspected PVC-induced cardiomyopathy, PVCs are ignored in situations other than bigeminy (in which case sinus beats and PVC beats are averaged).\textsuperscript{13} Our method correlates closely with echocardiography in assessing the non-PVC beats.

Among the 15 subjects, if we consider the LV function to be represented by the normal depolarization beats, including sinus, interrupted sinus, and post-PVC sinus beats, then subjects 6, 7, 9, 10, 13, and 15 would have normal function. Their burden of PVCs measured by PVC frequency was not significantly different from the remaining subjects with abnormal LVEF (Wilcoxon signed-rank test, \(P=0.23\)). If we instead consider the average EF of all beats as the representation of LV function, only subjects 9 and 10 would have normal function. These 2 subjects had high burdens of PVCs (35% and 33%) but they were the 2 latest occurring PVCs (675 and 766 ms after the previous R-wave, respectively). These PVCs produced SVs that were similar to sinus beats, which limited the hemodynamic effect of the PVCs. The PVC contribution to hemodynamics coupled with PVC frequency may be more important than frequency alone. For example, subject 6 had a PVC prevalence of 40% to 50%, but all the PVCs produced considerable SV, whereas subject 7 had a prevalence of 33% with PVCs that produced little SV. It is believed that PVC-induced cardiomyopathy develops in a time-dependent fashion where the cumulative burden over time may play an important role.\textsuperscript{14} Future longitudinal work examining the effect of hemodynamics and frequency is needed.

It has long been recognized that PVC burden is only one of the many factors contributing to impairment of LV systolic function in PVC-induced cardiomyopathy. PVC interpolation has been identified as an additional independent predictor, but the hemodynamic mechanism has not been elucidated.\textsuperscript{15} In 1 subject with interpolated PVCs, we observed the SVs of both the PVC and the post-PVC contraction being impaired. This has not been previously reported, and the implication of this finding would need to be investigated in a larger sample.

Previously, it has been reported that PVCs with coupling intervals \(\leq 600\) ms have a lower mean LVEF,\textsuperscript{16} but a recent study suggests that a longer coupling interval leads to more dyssynchronous contraction.\textsuperscript{17} Our study has shown a poor correlation between the coupling intervals of the PVC and the SV produced. This might be because of the heterogeneity of our subject population, including key factors, such as the origin of the PVC, the degree of dyssynchrony associated with the PVC contraction, and the degree of underlying...
cardiomyopathy. Future studies are needed to further examine this relationship using this technique.

**Clinical Relevance of the Technique**

A variety of mechanisms have been proposed for PVC-induced cardiomyopathy, including hemodynamic impairment, alterations in the heart rate, vascular autonomic dysregulation, increased oxygen consumption, ventricular dyssynchrony, tachycardia-induced cardiomyopathy, or alterations in calcium and ionic currents, but the underlying cause of PVC-induced cardiomyopathy remains unclear. Animal pacing models have also been used to better understand the myocardial dysfunction caused by PVCs. These models have found changes in global LV dimensions and function after 2 to 4 weeks of pacing with bigeminy that were programmed with a short coupling interval. These animal models suggest that PVCs can cause a reversible cardiomyopathy in structurally normal hearts, but the question of what differentiates benign PVCs and myopathy-causing PVCs remains unanswered.

Our approach may allow us to understand the hemodynamic features of PVCs better as the patients with the same frequencies might have a different hemodynamic profile of the PVCs. In addition, this technique may allow for improved patient selection for PVC ablations as eliminating low-SV PVCs might be more beneficial. Finally, some patients with frequent PVCs and preserved EF may have a subclinical cardiomyopathy as demonstrated by abnormal radial strain, which has been recently corroborated in animal models. Our approach may provide another means to identify subclinical cardiomyopathy, which might lead to earlier initiation of care and avoid the development of an overt cardiomyopathy.

To understand the hemodynamics of other arrhythmias, such as atrial fibrillation, pacing models of otherwise healthy, instrumented animals have been previously developed.

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**Figure 6.** Left ventricular function with interpolated premature ventricular complexes (PVCs). The ECG (A) and 2-dimensional plot (B) depict 4 beat types: sinus rhythm (C), post-PVC sinus (D), interrupted sinus (E), and the interpolated PVC contractions (F). Global volume quantification suggests that interpolated PVCs affect post-PVC loading and do not result in substantial stroke volume. Global volume measurements are found in Table 1 (patient 8).
Our technique allows for evaluation of patients without the need for instrumentation as the ECG system, and the imaging can be used to obtain both timing and hemodynamic information.

We only observed 30% of subjects who had increased (>5%) EF after ectopic contractions, whereas previous work describes substantial postextrasystolic potentiation. This discrepancy may be because of different patient population or measurement techniques.

Advantages Over Current Techniques

The 2D real-time imaging method we used combines non-Cartesian k-space sampling and an iterative SENSE-based image reconstruction technique to improve the image quality (by reducing undersampling artifacts) and spatiotemporal resolution when compared with conventional real-time acquisitions. This allows for accurate estimation of slice and global volumes in sinus rhythm patients when compared with standard cine acquisitions.5,6

In the patients with infrequent PVCs, our approach provided arrhythmia rejection similar to clinical CMR acquisitions where only the predominant contraction mode was quantified. However, our approach is more robust as conventional arrhythmia rejection can fail in several ways. First, conventional arrhythmia rejection uses the RR duration to categorize beats in real time and may have variable success depending on the ectopic morphology and frequency. Second, if the RR duration acceptance window is too small, multiple coupling intervals (as shown in Figures 3–6). In addition, recent publications indicate that the effect of respiratory position on LV volume quantification is negligible potentially because of a predominant in-plane as opposed to through-plane motion.27 However, changes in intrathoracic pressure will affect cardiac loading, and therefore, imaging during breathholds or selection of images based on respiratory motion could be used in future studies to minimize this effect.

A third limitation is that our approach may combine data acquired from different PVC beats, which occur with similar coupling intervals and PVC duration. Additional refinements to the technique are necessary to subdivide these clusters into unique PVC types.

In addition, our approach does not include retrospective reconstruction of motion corrected data, compressed sensing reconstructions, or low-rank image reconstruction, which have been recently proposed to further improve spatiotemporal resolution and image quality.28–31 These techniques are complementary to the method described here, and combination of those methods with this approach may allow further acceleration and improved image quality.

Table 2. Intraobserver and Interobserver Variability in Measurement of Slice $V_{max}$ and $V_{min}$

<table>
<thead>
<tr>
<th>Cardiac Phase</th>
<th>Intraobserver</th>
<th>Interobserver</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{max}$</td>
<td>CoV, %</td>
<td>Pearson Coefficient</td>
</tr>
<tr>
<td></td>
<td>6.5</td>
<td>0.982</td>
</tr>
<tr>
<td>$V_{min}$</td>
<td>8.0</td>
<td>0.988</td>
</tr>
</tbody>
</table>

CoV indicates coefficient of variation.
Sources of Funding
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Disclosures
None.

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