Myocardial performance is reduced immediately prior to ventricular ectopy

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BACKGROUND We recently demonstrated local voltage potentials indicating conduction impairment and block in the sinus beats preceding ventricular premature beats (VPBs) originating in the ventricular outflow tracts.

OBJECTIVE The purpose of this study was to test the hypothesis that impairment of impulse conduction would also lead to changes in the contractile performance of sinus beats preceding ventricular ectopy using Tissue Doppler echocardiography.

METHODS Twenty-three consecutive patients with VPBs were examined in the apical 4-chamber view with a frame rate of 150 Hz (GE VIVID VII). Eleven patients had no structural heart disease, 5 had dilated cardiomyopathy, 4 had ischemic heart disease, 2 had arrhythmogenic right ventricular dysplasia, and 1 had aortic stenosis. The ectopy originated in the ventricular outflow tracts in 15 patients and in the left ventricle 8. Eleven of the patients underwent radiofrequency ablation of the VPBs.

RESULTS Tissue Doppler imaging demonstrated a highly statistically significant decrease in myocardial performance in the last sinus beat before the VPB compared to earlier sinus beats. Thus, ejection time (time to peak end-systolic contraction) and peak systolic velocity shortened significantly (P < .001 for both) with a subsequent reduction in systolic shortening (end-systolic displacement; P < .001).

CONCLUSION Ventricular ectopy is preceded by a significant decrease in myocardial performance in the last sinus beat preceding VPBs as observed in consecutive patients with a broad variety of heart conditions pointing to a mutual underlying electrical mechanism (ie, localized conduction block confined to an area surrounding the ectopic pacemaker).

KEYWORDS Cardiomyopathy; Conduction impairment; Tissue Doppler imaging; Ventricular premature beats

ABBREVIATIONS TDI = tissue Doppler imaging; VPB = ventricular premature beat; VT = ventricular tachycardia

Introduction

We recently demonstrated discrete, local, fragmented voltage potentials suggesting conduction impairment and local conduction block in sinus beats preceding ventricular premature beats (VPBs) and ventricular tachycardia (VT) originating in the ventricular outflow tracts.1 During sinus rhythm, the potentials were recorded within the QRS complex in ventricular electrograms recorded close to the site of origin of the arrhythmias. Using tissue Doppler echocardiography (tissue Doppler imaging [TDI]), we investigated whether impairment of conductivity could lead to changes in the contractile performance of sinus beats preceding ventricular ectopy.

Methods

Patients

The study population consisted of 23 consecutive patients (Table 1). Eleven of the patients were referred for radiofrequency catheter ablation of frequent VPBs and/or VT, and 12 patients were referred for echocardiography and showed frequent VPBs at the time of examination. Eleven patients had no structural heart disease, 5 had dilated cardiomyopathy necessitating cardiac resynchronization therapy in 2, 4 had ischemic heart disease, 2 had arrhythmogenic right ventricular dysplasia, and 1 had aortic stenosis. The VPBs/VT was located in the right ventricle in 15 patients, most frequently within the septum of the right ventricular outflow tract. In the remaining 8 patients, the arrhythmias originated from the left ventricle, frequently in the inferoseptal area.

Tissue Doppler echocardiography

All patients underwent echocardiographic investigation including tissue Doppler imaging (TDI). The examination was performed with the GE VIVID VII (General Electric...
GE Medical, Milwaukee, WI, USA). We previously reported on the use of TDI for evaluation of myocardial performance as well as changes in myocardial function. We found that the technique was robust and reproducible, and annular systolic displacement was closely related to cardiac output.2

Patients were examined from the apical 4-chamber view with a frame rate of 160 Hz. Loops containing at least 3 sinus beats prior to a VPB were obtained during quiet breathing. Analyses were performed off-line using custom-designed software (GE EchoPac BT06, GE Medical, Milwaukee, WI, USA). Left ventricular systolic function was assessed using 3 parameters: left ventricular ejection time, mitral annular peak systolic velocity, and longitudinal displacement. Regions of interest were positioned just above the mitral annulus in the interventricular septum and lateral wall. All measurements were done during end-systole. Importantly, we applied drift compensation with truncation to zero after each cardiac cycle.

The following notation was used (Figure 1):
- S_1: Last sinus beat before a VPB/VT
- S_2: Second last sinus beat before a VPB/VT
- S_3: Third last sinus beat before a VPB/VT
- S_i: ith last sinus beat before a VPB/VT

### Statistical analysis
To investigate the difference between the amplitude of the first to fourth sinus beat before the VPB, a linear mixed model with a random effect for the individual patient was used. This was done to accommodate the inherent correlation in repeated measures taken on the same patients. We tested whether clinical characteristics of subpopulations (males vs females, ischemic vs nonischemic heart disease, or between patients with VT vs those without VT) influenced the results by placing these variables in the model one at a time. $P < .05$ was considered significant. All statistical analyses were performed using SAS for Windows (version 9.1.3, SAS Institute Inc, Cary, NC, USA).

### Table 1 Clinical characteristics of the study subjects

<table>
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<tr>
<th>Patient no.</th>
<th>Age (y)</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Arrhythmia</th>
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<td>1</td>
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<td>RVOT</td>
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<td>RVOT</td>
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<tr>
<td>4</td>
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<td>VPB + VT</td>
<td>RVOT</td>
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<tr>
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<tr>
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<tr>
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</tr>
<tr>
<td>10</td>
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<td>M</td>
<td>IHD</td>
<td>VPB</td>
<td>LV</td>
</tr>
<tr>
<td>11</td>
<td>66</td>
<td>M</td>
<td>IHD</td>
<td>VPB</td>
<td>LV</td>
</tr>
<tr>
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<td>25</td>
<td>M</td>
<td>AS</td>
<td>VPB</td>
<td>RVOT</td>
</tr>
<tr>
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<td>DCM</td>
<td>VPB</td>
<td>RVOT</td>
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<tr>
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<tr>
<td>23</td>
<td>76</td>
<td>M</td>
<td>IHD</td>
<td>VPB + VT</td>
<td>LV</td>
</tr>
</tbody>
</table>

Patients are listed in order of enrollment.

ARVD = arrhythmogenic right ventricular dysplasia; AS = aortic stenosis; DCM = dilated cardiomyopathy; IHD = ischemic heart disease; LV = left ventricle; RVOT = right ventricular outflow tract; SHD = structural heart disease; VF = ventricular fibrillation; VPB = ventricular premature beat; VT = ventricular tachycardia.

*Patient received cardiac resynchronization therapy due to heart failure.

**Figure 1** Standard ECG leads I–III and V1. S-1, S-2, S-3, and S-4 are the last four sinus beats before the ventricular premature beat (VPB), respectively.
Results

Baseline characteristics of the study subjects are listed in Table 1. TDI demonstrated a highly significant decrease in left ventricular ejection time (15%, \( P < 0.0001 \)), peak myocardial velocity (41% in interventricular septum and 41% in lateral wall, \( P < 0.0001 \)), and longitudinal systolic displacement (42% in interventricular septum and 39% in lateral wall, \( P < 0.0001 \)) in S-1 compared to S-2, S-3, and S-4 (Table 2 and Figures 2 and 3). There were no statistical differences between S-2 and S-3, and S-3 and S-4.

Regardless of the origin of the VPB, longitudinal systolic shortening was reduced equally in the septum and lateral wall. Of note, all patients systematically showed a reduction in TDI measures before the VPB, and contractile response was always the same within patients. We did not find any difference in the results between males vs females, ischemic vs nonischemic heart disease, or between patients with VT vs those without VT.

To rule out potential methodologic bias, we introduced programmed properly timed single VPBs via the right ventricular pacing lead placed in the septal area of the outflow tract in patient 23, who had a dual-chamber implantable cardioverter-defibrillator placed with the ventricular lead in the high interventricular septum. Paced VPBs were introduced with coupling intervals similar to the coupling intervals of the spontaneous VPBs. For the spontaneous VPBs, a decrease in end-systolic shortening was observed in S-1 (7.8 mm) compared to S-2 (11.0 mm) and S-3 (10.0 mm). With the paced VPBs no difference was observed (S-1 = 10.3 mm vs S-2 = 8.8 mm and S-3 = 10.0 mm; Figure 4).

Discussion

The most important and novel finding of the present study was the highly significant decrease in myocardial performance in the sinus beat S-1 preceding the VPBs compared to earlier sinus beats (S-2, S-3, . . . S-i) manifested by the impairment in left ventricular ejection time, peak velocity, and longitudinal shortening. The decrease was most pronounced for peak velocity and longitudinal shortening, which was reduced to half.

The explanation and mechanisms behind the reduction in myocardial performance are uncertain. We speculate that the reduction in myocardial performance is caused by impaired electrical conduction and conduction block of the electrical impulse of S-1, confined to an area surrounding the ectopic pacemaker focus thereby protecting the ectopic pacemaker. This assumption is based on recent findings in 25 patients, 9 of whom are included in this series, with VPBs and VT originating in the ventricular outflow tracts undergoing radiofrequency catheter ablation. During sinus rhythm, discrete local and fragmented voltage potentials were recorded close to the site of the ectopic pacemaker, 15–85 ms after the onset, and within the QRS complex, in 24 of the 25 patients studied. In contrast, the same potential was demonstrated 30–50 ms prior to the QRS complex of the sinus rhythm, suggesting that these potentials are related to the VPB.
the VPB (Figure 5). The local potentials of the sinus beats may represent slow and impaired anterograde conduction in the area surrounding the ectopic pacemaker resulting in altered and impaired myocardial performance, and the local potential of the VPB may be the result of retrograde conduction of the electrical impulse originating within the protected pacemaker of the VPB. A graphic representation of the proposed mechanism is depicted in Figure 5. However, this remains purely speculative and further research is needed.

In this study, approximately half of the patients displayed VPBs and VT of unknown origin without structural heart disease; the other half of the patients had structural heart disease and VPBs also originating from the left ventricle. Despite these possible differences in the mechanisms of the arrhythmias, we found the same difference in the relative decrease in S-1, suggesting a common mechanism in all study subjects.

Recent studies investigating dispersion of connexin43 in different areas of the myocardium provides a common arrhythmia mechanism for triggered as well as reentrant arrhythmias and are coherent with the findings in our study. Connexin43 gap junction concentrations have been shown to be decreased in ischemic myocardial areas resulting in high automaticity and slow conduction in these areas, and chimeric connexin43+/− mice have a high incidence of ventricular ectopy but not sustained VT. Connexin43 is also absent in sinoatrial tissue and AV nodal tissue, which, along with HCN4 expression, probably account for the high automaticity of these tissues. Differences in connexin distribution and concentration might provide a theory for a common mechanism of VPBs in different heart diseases, even though this has not been investigated in this study and remains speculative. Of interest, chimeric connexin43+/− mice show focal areas of slowed conduction and a lowered systolic function without dilation or hypertrophy. The authors ascribe this phenomenon as secondary to dyssynchronous contraction caused by slowed conduction rather than the slowed conduction itself.

Of note, the evidence of failed local conduction noted in right ventricular outflow tract VT is not inconsistent with triggered activity as the responsible mechanism for this tachycardia. Loss of conduction during sympathetic nervous system stimulation would result in prolongation of the diastolic interval and further accumulation of calcium into the sarcoplasmic reticulum, thereby encouraging spontaneous calcium release that could trigger a transient inward current through the sodium–calcium exchanger. Indeed, recent work suggests that even sinus node automaticity may...
be largely driven by a calcium-mediated inward current analogous to a delayed afterdepolarization.  

In 2 of the 5 patients with dilated cardiomyopathy (patients 13 and 18), the condition was most likely caused by frequent VPBs. Patient 13 (ejection fraction 25%) suffered from very frequent VPBs for more than 10 years and on Holter monitoring disclosed 33,000 VPBs per 24 hours. One year after successful ablation, her ejection fraction increased to 50%. Similarly, patient 18, who had dilated cardiomyopathy and ejection fraction 20%, had left bundle branch block and was in New York Heart Association functional class III despite optimal medical therapy. He received treatment with cardiac resynchronization therapy–defibrillator but did not respond. During follow-up, 25%–30% VPBs were documented by the read-out memory of the device. Subsequently, the patient underwent radiofrequency catheter ablation, and his ejection fraction increased to 45%, 3 months after the procedure. Previous reports have documented that the frequency of ventricular ectopic activity is an important determinant for the development of cardiomyopathy and that successful radiofrequency catheter ablation can result in significant improvement of ejection fraction.9–11 Furthermore, frequent VPBs can result in interventricular and intraventricular mechanical dyssynchrony12 and be the cause of nonresponsiveness to cardiac resynchronization therapy.13 The decreased myocardial performance present in S1 may also cause this beat to become dysynchronous, thereby contributing to the development of dilated cardiomyopathy in patients with frequent ventricular ectopy. The reduction in myocardial performance induces remodeling and may also contribute to the development of “tachycardia-induced cardiomyopathy.”

Conclusion
The present study is observational and demonstrates for the first time that ventricular ectopy is preceded by a significant decrease in myocardial performance in the last sinus beat preceding the VPB. The mechanism behind the impairment is not clear. The phenomenon was observed in consecutive patients with a broad variety of heart conditions, which points to a shared underlying mechanism (ie, localized electrical conduction block confined to an area surrounding the ectopic pacemaker).

References