Myocardial performance is reduced immediately prior to ventricular ectopy

Poul Erik Bloch Thomsen, MD, PhD,* Thomas Fritz Hansen, MD,* Christian Jons, MD,† Thue Olsen, MD,* Arne Johannessen, MD, PhD,* Knud Særmark, MSc, PhD,‡ Scott McNitt, MS,† Mark Haigney, MD,¶ Peter Sogaard, MD, PhD*

*From the *Cardiology Department P, Gentofte University Hospital, Copenhagen, Denmark, †The Heart Research Follow Up Program, University of Rochester Medical Center, Rochester, New York, ‡Department of Physics, Technical University of Denmark, Lyngby, Denmark, and ¶Department of Medicine, Uniformed Services University, Bethesda, Maryland.*

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

(Heart Rhythm 2012;9:86–90)

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.

Address reprint requests and correspondence: Dr. Poul Erik Bloch Thomsen, Cardiology Department, Gentofte University Hospital, Niels Andersensvej 65, 2900 Copenhagen, Denmark. E-mail address: pebt@geh.regionh.dk.

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

1547-5271/$ -see front matter doi:10.1016/j.hrthm.2011.08.023

Table 1 Clinical characteristics of the study subjects

Patient no.	Age (y)	Gender	Diagnosis	Arrhythmia	Location
1	52	F	No SHD	VPB+VT	RVOT
2	58	F	No SHD	VPB	RVOT
3	58	F	No SHD	VPB	RVOT
4	54	M	No SHD	VPB+VT	RVOT
5	63	F	No SHD	VPB	RVOT
6	58	F	No SHD	VPB+VT	RVOT
7	31	F	No SHD	VPB+VT	RVOT
8	49	M	No SHD	VPB+VT	RVOT
9	20	F	ARVD	VPB+VT/VF	RVOT
10	67	M	IHD	VPB	LV
11	66	M	IHD	VPB	LV
12	25	M	AS	VPB	RVOT
13	63	F	DCM	VPB	RVOT
14	45	F	No SHD	VPB+VT	RVOT
15	50	M	ARVD	VPB	RVOT
16	64	M	No SHD	VPB	RVOT
17	89	M	IHD	VPB	LV
18*	67	M	DCM	VPB+VT	LV
19*	76	M	DCM	VPB	LV
20	85	M	DCM	VPB	LV
21	57	M	DCM	VPB	LV
22	55	F	No SHD	VPB	RVOT
23	76	M	IHD	VPB+VT	LV

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.

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 customized 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} *i*th 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).

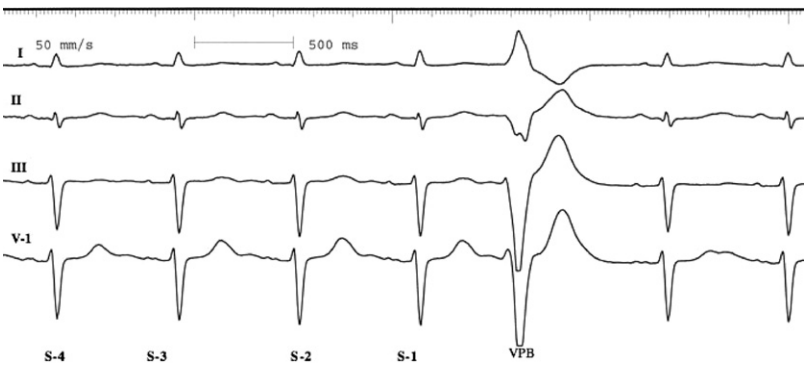

Figure 1 Standard ECG leads I–III and V_1. S-1, S-2, S-3, and S-4 are the last four sinus beats before the ventricular premature beat (VPB), respectively.

Table 2 Results from tissue doppler echocardiography

	S-1	S-2	S-3	S-4
Longitudinal shortening (mm)				
IVS	5.3*	8.6	8.8	9.6
LAT	5.8*	9.0	9.6	10.0
Velocity (cm/s)				
IVS	3.0*	4.8	4.8	5.3
LAT	3.2*	5.1	5.1	5.4
Left ventricular ejection time (ms)	227.4*	265.6	267.3	272.6

Average values from measurements on all study subjects are shown.
IVS = intraventricular septum; LAT = lateral wall.
*Values are different from all other values tested individually, with $P <$ .001. There were no significant difference between S_{-2}, S_{-3}, and S_{-4}.

Results

Baseline characteristics of the study subjects are listed in Table 1. TDI demonstrated a highly significant decrease in left ventricular ejection time (15%, $P <$.0001), peak myocardial velocity (41% in interventricular septum and 41% in lateral wall, $P <$.0001), and longitudinal systolic displacement (42% in interventricular septum and 39% in lateral wall, $P <$.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.[1] 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

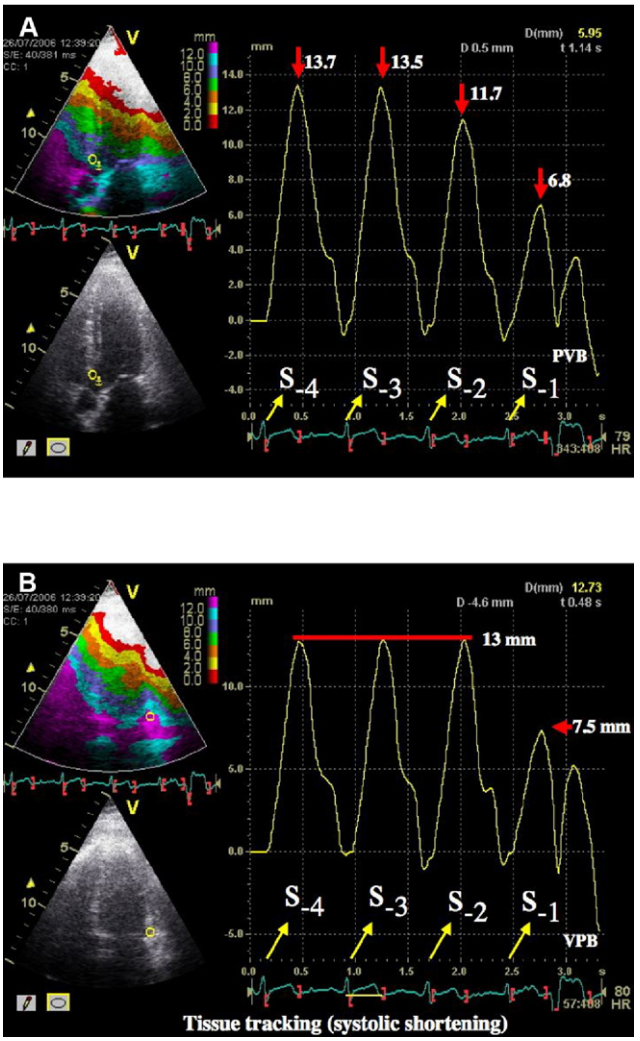

Figure 2 Patient 9. **A:** Tissue tracking image with the region of interest positioned in the basal part on the intraventricular septum. Systolic longitudinal shortening on the region of interest is displaced in sinus beats S_{-4} to S_{-1} prior to the ventricular premature beat (VPB). In S_{-1} and S_{-2}, a decrease in longitudinal systolic shortening occurs compared to S_{-3} and S_{-4} (13.7, 13.5, 11.7 to 6.8 mm). **B:** Region of interest position in the basal part of the lateral wall. Systolic longitudinal shortening decreases only in S_{-1} compared to S_{-2}, S_{-3}, and S_{-4}, and the shortening is comparable to the systolic longitudinal shortening of the VPB in the intraventricular septum.

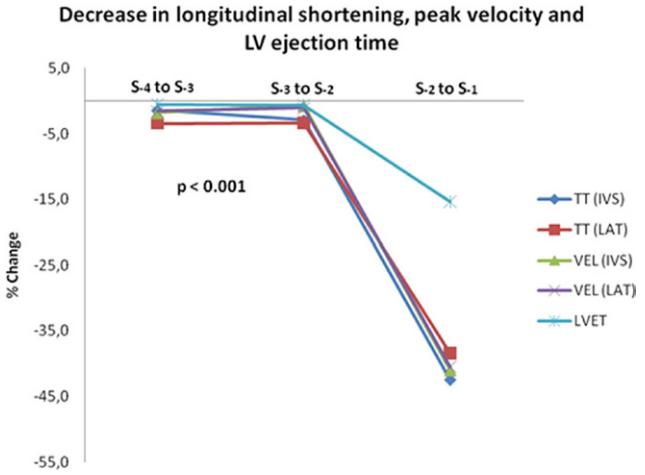

Figure 3 Results of tissue Doppler echocardiography in the four sinus beats preceding a ventricular premature beat. Peak systolic myocardial velocity and longitudinal shortening are decreased by approximately 40%, and left ventricular (LV) ejection time is decreased by 15%. There were no differences in the lateral or septal measurements regardless of the location of the ectopic focus. IVS = intraventricular septum; LAT = lateral wall; TT = tissue tracking.

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,[3] 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,[4] and chimeric connexin43$^{+/-}$ mice have a high incidence of ventricular ectopy but not sustained VT.[5] Connexin43 is also absent in sinoatrial tissue[6] and AV nodal tissue,[7] 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.[6] 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.[3] 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

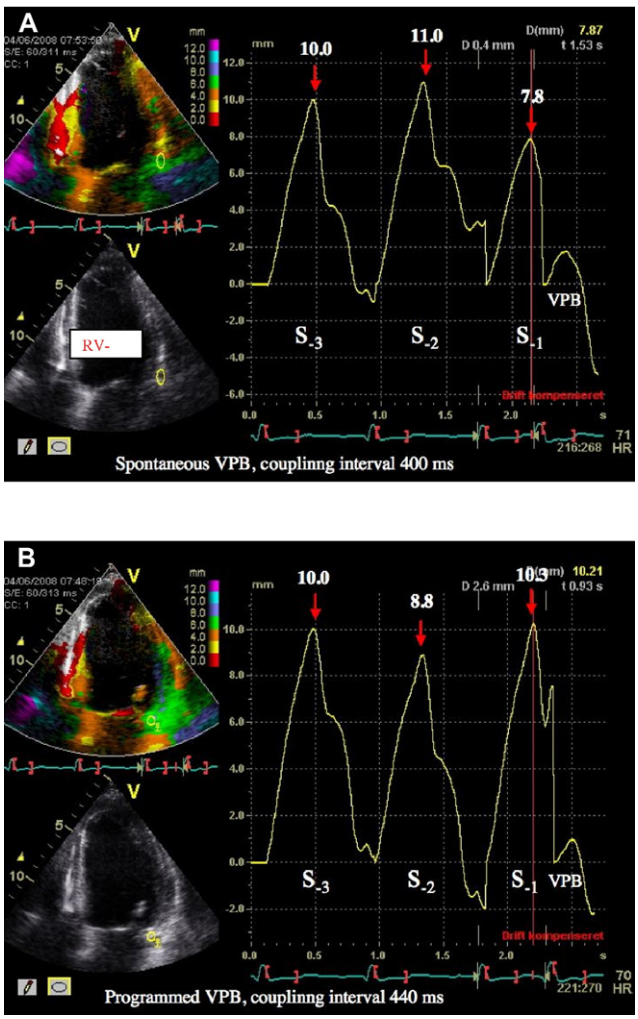

Figure 4 Comparison of longitudinal shortening of S_{-1} between a spontaneous ventricular premature beat (VPB) and a paced VPB with identical coupling intervals in patient 23. The patient had a CRT-D device implanted with the right ventricular coil electrode screwed into the right ventricular septum (RV-lead), and simultaneous biventricular pacing was performed. **A:** Spontaneous VPB with coupling interval of 400 ms showing a decrease in longitudinal systolic shortening of S_{-1} compared to S_{-2}, and S_{-3} (7.8, 11.0, to 10.0 mm). **B:** Single paced VPB is introduced with a coupling interval of 440 ms. There is no decrease in systolic shortening of S_{-1} compared to S_{-2}, and S_{-3}, (10.3, 8.8, and 10.0). See text for further discussion.

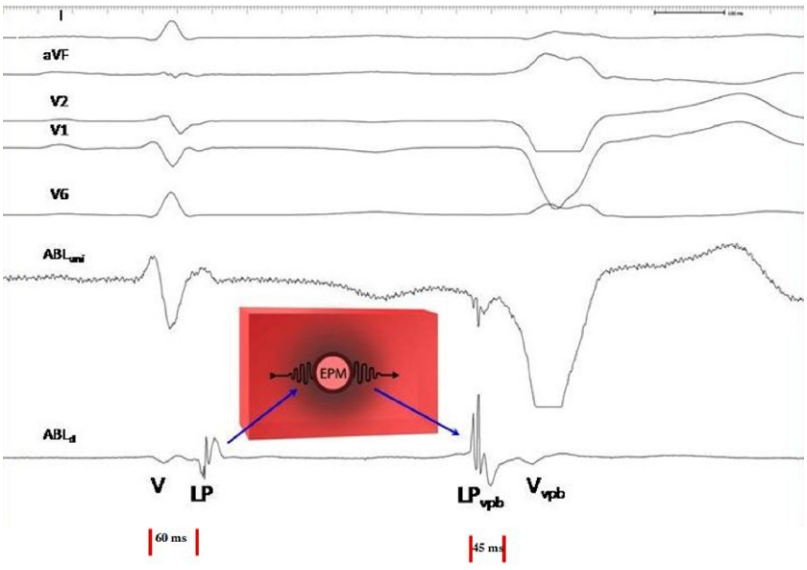

Figure 5 Schematic illustration of the suggested mechanism of the prearrhythmic reduction in myocardial performance in patient 5. Standard ECG recordings and intracardiac electrograms recorded during radiofrequency ablation with the ablation catheter positioned close to the ectopic pacemaker (EPM). Shown are standard ECG leads I, aVF, V_2, V_1, and V_6. The ablation catheter records an amplified unipolar (ABL uni) and bipolar electrogram (ABL d). Two local voltage potentials (LP and LP_{vpb}) are present, indicating impaired electrical conduction. The LP potential is recorded 60 ms after the onset and within the QRS complex of the last sinus beat (S_{-1}) and the local ventricular potential (V_{-1}), whereas LP_{vpb} is recorded 45 ms prior to the QRS complex of the VPB *(vertical red lines)*. The *red box* illustrates the EPM surrounded by an area of depressed conductivity *(gray shaded area)*. S_{-1} is conducted into the zone of impaired conduction *(blue line)* and probably is blocked. As a consequence, the contraction also is impaired, resulting in a decrease in ejection time, peak systolic velocity, and longitudinal shortening of S_{-1}. The EPM is protected by entrance block from the sinus impulse and therefore can fire and depolarize the zone of slow conduction in the opposite direction *(blue line)* leading to LP_{vpb} giving rise to the QRS complex of the VPB. See text for further discussion.

be largely driven by a calcium-mediated inward current analogous to a delayed afterdepolarization.[8]

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 dyssynchrony[12] and be the cause of nonresponsiveness to cardiac resynchronization therapy.[13] The decreased myocardial performance present in S_{-1} may also cause this beat to become dyssynchronous, 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

1. Bloch Thomsen PE, Johannessen A, Jons C, et al. The role of local voltage potentials in patients with outflow tract ectopy. Europace 2010;12:850–860.
2. Valeur N, Fritz-Hansen T, Risum N, Mogelvang R, Bloch Thomsen PE, Sogaard P. Echocardiographic effects of changing atrioventricular delay in cardiac resynchronization therapy based on displacement. J Am Soc Echocardiogr 2010;23:621–627.
3. Lerman BB. Mechanism of outflow tract tachycardia. Heart Rhythm 2007;4:973–976.
4. Lerner DL, Yamada KA, Schuessler RB, Saffitz JE. Accelerated onset and increased incidence of ventricular arrhythmias induced by ischemia in Cx43-deficient mice. Circulation 2000;101:547–552.
5. Gutstein DE, Danik SB, Lewitton S, et al. Focal gap junction uncoupling and spontaneous ventricular ectopy. Am J Physiol Heart Circ Physiol 2005;289:H1091–H1098.
6. Coppen SR, Kodama I, Boyett MR, et al. Connexin45, a major connexin of the rabbit sinoatrial node, is co-expressed with connexin43 in a restricted zone at the nodal-crista terminalis border. J Histochem Cytochem 1999;47:907–918.
7. Efimov IR, Nikolski VP, Rothenberg F, et al. Structure-function relationship in the AV junction. Anat Rec A Discov Mol Cell Evol Biol 2004;280:952–965.
8. Maltsev VA, Vinogradova TM, Lakatta EG. The emergence of a general theory of the initiation and strength of the heartbeat. J Pharmacol Sci 2006;100:338–369.
9. Firsovaite V, De SJ, Duytschaever M, Tavernier R. Frequent ventricular premature beats: a reversible cause of cardiomyopathy? Acta Cardiol 2006;61:573–576.
10. Takemoto M, Yoshimura H, Ohba Y, et al. Radiofrequency catheter ablation of premature ventricular complexes from right ventricular outflow tract improves left ventricular dilation and clinical status in patients without structural heart disease. J Am Coll Cardiol 2005;45:1259–1265.
11. Bogun F, Crawford T, Reich S, et al. Radiofrequency ablation of frequent, idiopathic premature ventricular complexes: comparison with a control group without intervention. Heart Rhythm 2007;4:863–867.
12. Kass DA. Ventricular resynchronization: pathophysiology and identification of responders. Rev Cardiovasc Med 2003;4(Suppl 2):S3–S13.
13. Herczku C, Kun C, Edes I, Csanadi Z. Radiofrequency catheter ablation of premature ventricular complexes improved left ventricular function in a non-responder to cardiac resynchronization therapy. Europace 2007;9:285–288.