Premature ventricular contractions of the right ventricular outflow tract: is there an incipient underlying disease? New insights from a speckle tracking echocardiography study

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**A B S T R A C T**

**Context:** Premature ventricular contractions (PVCs) originating in the right ventricular outflow tract (RVOT) are traditionally considered idiopathic and benign. Echocardiographic conventional measurements are typically normal.

**Aims:** To assess whether right ventricle longitudinal strain, determined by two-dimensional speckle tracking echocardiography, differ between RVOT PVCs patients (treated with catheter ablation) and healthy controls.

**Methods:** We retrospectively selected patients with PVCs from the RVOT who underwent electrophysiological study and catheter ablation between 2016 and 2019. Patients with documented structural heart disease were excluded. Transthoracic echocardiography was performed and right ventricle global longitudinal strain (RV-GLS), free wall longitudinal strain (RVFW-LS) and left ventricle global longitudinal strain (LV-GLS) were determined as well as conventional ultrasound measurements of RV and LV function.

**Results:** We studied 21 patients with RVOT PVCs and 13 controls. Patients with PVCs from the RVOT had lower values of RV-GLS and RVFW-LS compared with the control group (−19.4% versus −22.5%, P = 0.015 and −22.1% versus −25.5, P = 0.041, respectively). They also had lower values of LV-GLS, although still within the normal range (−19.1% versus −20.9%, P = 0.047). Regarding RVOT PVCs patients only, RV-GLS and RVFW-LS had no correlation with the PVCs burden prior to catheter ablation and they did not differ between the patients in whom the catheter ablation was successful and those in whom it was not. RV-GLS also had a positive correlation with RVOT proximal diameter (r = 0.487, P = 0.025).

**Conclusions:** In this group of RVOT PVCs patients, we found worse RV longitudinal strain values (and therefore sub-clinical myocardial dysfunction) when compared to healthy controls.

**1. Introduction**

Premature ventricular contractions (PVCs) originating in the right ventricular outflow tract (RVOT) are traditionally considered idiopathic and benign in the absence of structural heart disease [1]. However, there is evidence that a percentage of these patients may present with polymorphic ventricular tachycardia or ventricular fibrillation [2,3]. Cardiac magnetic resonance (CMR) imaging studies involving patients with idiopathic RVOT PVCs had contradictory results, with some reporting no pathological findings and others reporting structural abnormalities such as wall bulging, focal wall thinning and fatty replacement [4–6]. From an electro-anatomical mapping perspective, it has recently been demonstrated that patients with PVCs from the RVOT and apparently normal hearts have areas of low voltage electrograms in the RVOT [7]. Using non-invasive approaches, with endocardial and epicardial mapping systems to study the electrophysiological properties of the RVOT, it has been found that recovery time (RT) was shorter...
and activation recovery interval (ARI) dispersion across the epicardium was higher in patients with RVOT PVC versus control patients [8]. It is then reasonable to question if in RVOT PVCs patients, along with an apparent electrical remodeling process there is also an anatomical substrate behind the PVCs.

The quantification of right heart chamber size and function by echocardiography has been challenging due to the complex anatomy of the right ventricle (RV) [9]. Recently, two-dimensional speckle tracking echocardiography (2D-STE), an angle-independent technique that quantifies the amount of myocardial deformation, based on speckles (natural acoustic markers) and their motion in consecutive frames, has been under special attention. It was initially introduced to study the left ventricle (LV) function, but it is currently being applied to evaluate other cardiac chambers. It has the ability to detect subtle myocardial dysfunction earlier, in sub-clinical states, and has already proven its prognostic significance in different cardiomyopathies, such as hypertrophic cardiomyopathy [10]. Recent reports have shown that RV function can be accurately assessed by this method [11].

The aim of our study was to assess whether RV longitudinal strain, determined by 2D-STE, differs between RVOT PVCs patients and healthy controls.

2. Methods

2.1. Study population

We conducted a retrospective single-center analysis of 21 patients with frequent PVCs from the RVOT, defined as more than 10% of the total beats per 24 h, who underwent electrophysiological study and catheter ablation between 2016 and 2019. Patients with previous history of atrial fibrillation, documented structural heart disease (by transthoracic echocardiography and/or cardiac MRI), advanced lung disease or family history of sudden cardiac death or arrhythmogenic right ventricular cardiomyopathy (ARVC) were excluded. We also excluded patients with poor quality speckle tracking images defined as more than 2 segments with inappropriate tracking in a single view. We included, as a control group, 13 patients who underwent atrioventricular node reentrant tachycardia ablation in the same period of time, matched for age and sex, with a previous 24-hour Holter monitoring without PVCs.

2.2. Study design

We evaluated the demographic characteristics and cardiovascular risk factors of the patients such as hypertension, diabetes mellitus, dyslipidemia and smoking. Patients underwent a standard 12-lead ECG that included recordings of both premature ventricular and sinus rhythm beats using standard paper speed and calibration. A 24-hour Holter monitoring was performed before the catheter ablation, and the presence and number of PVCs was assessed. The location from where the PVCs were ablated was registered. The acute success rate of the catheter ablation procedure was defined as the absence of RVOT PVCs for at least 30 minutes after the procedure. Transthoracic echocardiography was performed between 30 and 60 days after the catheter ablation procedure, using a Vivid E95 ultrasound system (GE Healthcare®, Horten, Norway) equipped with a 1.7/3.4 MHz tissue harmonics transducer. A complete echocardiographic study using standard views (parasternal long- and short-axis, apical 4-, 2- and 3-chamber, and RV-focused 4-chamber) was performed, during breath-holding and with stable electrocardiographic recording. Image contrast, frequency, depth and sector width were adjusted to optimize image acquisition. Three consecutive heart cycles (all of the patients were in sinus rhythm) were acquired. Data was digitally recorded for off-line analysis using dedicated software (EchoPAC 9.0, GE Healthcare®, Horten, Norway). Left ventricular ejection fraction (LVEF) was evaluated by the modified Simpson’s biplane method, after determination of left ventricular end-diastolic (LVEDV) and end-systolic volumes (LVESV). RVOT proximal and distal diameters were measured from the parasternal short-axis (PSAX) view (Fig. 1). Left atrial volume (LAV) was determined by the modified biplane method and right atrial (RA) area was measured in the 4-chamber view. Longitudinal RV function was assessed using tricuspid annular plane systolic excursion (TAPSE) and tricuspid annular peak systolic velocity (S’). End-diastolic and end-systolic RV areas were obtained and fractional area change (FAC) was calculated. Measurements were done according to the latest recommendations of the European Association of Cardiovascular Imaging (EACVI) [9]. For the speckle tracking analysis the reference frame coincided with the onset of the QRS. The frame rate was between 60 and 80 frames per second. The RV (in RV-focused 4-chamber view) and LV (in the 3 apical views) endocardial border was manually traced and the region of interest (ROI) was manually adjusted after analysis of tracking quality. RV global longitudinal strain (RV-GLS) was defined as the mean of the peak systolic strain in the 3 RV free wall segments and the ventricular septum (Fig. 2). RV free wall longitudinal strain (RVFW-LS) was defined as the mean of the peak systolic strain in the 3 RV free wall segments obtained from a 6-segment ROI. LV global longitudinal strain (LV-GLS) was defined as the mean of the peak systolic strain in the 16 LV segments. Analyses were performed in percentages.

2.3. Statistical analysis

SPSS version 22 software (SPSS Inc., Chicago, Illinois) was used for statistical analysis. A Kolmogorov-Smirnov test was performed to test for the normality of continuous variables and in the presence of normality data is expressed as mean and standard deviation (SD) and, in its absence, as median and interquartile range [IQR]. Data is presented as frequencies and percentages for categorical variables. Categorical variables were compared with the use of the chi-square test. Continuous variables were compared with the use of Student’s t-test or Mann Whitney test, as appropriate. Correlations between continuous variables were assessed by calculation of Pearson correlation coefficients. A value of $P < 0.05$ was considered statistically significant.

2.4. Ethics

The study was approved by the local Ethical Committee and is in accordance with the Helsinki Declaration. All participants or their legal representatives provided written informed consent.

3. Results

Twenty-one patients out of 37 were included in the RVOT PVCs group (Fig. 3) and 13 patients in the control group. Thirteen out of 21 patients had a cardiac MRI study done before the ablation procedure, which was normal in all of them. Median PVCs burden in the RVOT PVCs group prior to ablation was 16197 [9600–23213] PVCs in 24-hour Holter monitoring. The median time of PVCs before ablation was 18 [7–41] months. PVC precordial transition was in V3 in 3 patients (14%) and beyond V3 in 18 patients (86%). The ablation site was in the RVOT free wall in 5 patients (24%) and in the RVOT septum in 16 patients (76%). The acute success rate of the catheter ablation procedure, defined as absence of RVOT PVCs for at least 30 minutes after the procedure, was 86% (n = 18). The RVOT PVCs and the control group did not differ in relation to age.
gender, cardiovascular risk factors, body mass index, body surface area, heart rate, systolic and diastolic blood pressure during echocardiographic examination. Table 1 summarizes the baseline characteristics and Table 2 summarizes standard and strain echocardiographic parameters of RVOT PVCs patients and the control group. There were no significant differences between the groups concerning conventional echocardiographic measurements of RV and LV dimensions and function. Patients with RVOT PVCs
had lower values of RV-GLS and RVFW-LS compared with the control group (19.4% versus 22.5%, \(P = 0.015\) and 22.1% versus 25.5, \(P = 0.041\)) as well as lower values of LV-GLS (19.1% versus 20.9%, \(P = 0.047\)) (Table 2). Regarding RVOT PVCs patients only, RV-GLS, RVFW-LS and LV-GLS did not differ between the patients in whom the catheter ablation procedure was successful and those in whom it was not (19.5% versus 18.9%, \(P = 0.787\); 22.4% versus 20.8%, \(P = 0.668\) and 18.5% versus 19.2%, \(P = 0.677\), respectively). We also observed that the burden of PVCs prior to the catheter ablation procedure had no correlation with the RV-GLS, RVFW-LS and LV-GLS values obtained (\(r = -0.046, P = 0.866\); \(r = -0.266, P = 0.404\) and \(r = -0.165, P = 0.528\), respectively). The time between PVCs diagnosis and ablation did not correlate with post-ablation RV-GLS, RVFW-LS and LV-GLS values (\(r = 0.157, P = 0.496\); \(r = 0.120, P = 0.659\) and \(r = 0.404, P = 0.070\), respectively). In the RVOT PVCs group, when comparing RV-GLS and conventional echocardiographic measurements, we found that RV-GLS had a positive correlation with RVOT proximal diameter (\(r = 0.487, P = 0.025\)) (Fig. 4). RV-GLS also correlated with LV-GLS (\(r = 0.572, P = 0.007\)).

4. Discussion

Standard volumetric techniques and wall motion assessment usually used to assess LV function cannot be applied in the same manner to the RV due to its complex geometry, thin wall and different contraction pattern. In this study 2D-STE, an angle independent technique that detects sub-clinical myocardial dysfunction was used to track the relative movement of myocardial speckles, in two-dimensional gray-scale images, over multiple time frames. Saberniak et al. compared RVOT PVCs patients with ARVC patients (the 2010 Task Force Criteria were used to make a diagnosis of ARVC) and found that RV-GLS had a positive correlation with RVOT proximal diameter (\(r = 0.487, P = 0.025\)) (Fig. 4). RV-GLS also correlated with LV-GLS (\(r = 0.572, P = 0.007\)).
have suggested that certain patients with RVOT PVCs may develop what has been called arrhythmia induced cardiomyopathy — LV and/or RV dysfunction caused by the presence of a high burden of PVCs [13]. This cardiomyopathy is not a tachycardio-myopathy [14]. Our echocardiographic findings cannot be explained by dyssynchrony either because they subside after the ablation procedure.

As previously stated, Parreira et al. group already demonstrated, in their group of RVOT PVCs patients, the existence of abnormal electrophysiological characteristics in the RVOT [8]. The major finding of our study is that RV-GLS and RVFW-LS are significantly lower in patients with RVOT PVCs compared with the control group. Besides, the RV-GLS and RVFW-LS values we obtained for our RVOT PVCs population (−19.4 ± 4% and −22.1 ± 6%) were lower when compared to normal values described for healthy individuals. Muraru et al. group reported, in a study of 276 healthy volunteers, a lower limit of normal for 6-segment RV-GLS of −20.0% for men and −20.3% for women and a lower limit of normal for 3-segment RVFW-LS of −22.5% for men and −23.3% for women [15]. To the best of our knowledge, there are no echocardiographic studies that compared strain-derived parameters in RVOT PVCs patients with healthy subjects. Concerning strain values determined by CMR, Zghib et al. group have previously proved, in ARVC patients, that lower regional strain could identify low voltage areas on endocardial and epicaldial electroanatomical mapping and had a better correlation with VT substrate than late gadolinium enhancement sites [16].

We also found that LV-GLS was lower in the RVOT PVCs population compared with the control group, although it was still within the range of considered normal values for this 2D-STE parameter [17]. The lower RV-GLS, RVFW-LS and LV-GLS measurements were not correlated with the PVC burden before ablation nor with the acute success of the catheter ablation procedure. These results may suggest that the sub-clinical myocardial dysfunction detected might not be a consequence of the PVCs. However, without a baseline echocardiographic study before the occurrence of PVCs we cannot determine whether the mechanical abnormality is the result or the cause of the PVCs.

We also found a positive correlation between RV-GLS and RVOT proximal diameter determined in PSAX views — the lower the absolute values of RV-GLS the larger the dimension of the proximal RVOT (although the mean value of this diameter is still normal and outside the task force criteria for the diagnosis of ARVC). The reason for this is unknown. There are no echocardiographic reports in the literature describing morphologic abnormalities in the right heart of RVOT PVCs patients, although there are some CMR studies reporting abnormal findings. Gaita et al. observed that in a long term follow up of RVOT PVCs patients, 8 out of 11 had focal fatty replacement and other abnormalities of the right ventricle [18]. We may hypothesize that a larger RVOT is an early marker of an incipient cardiomyopathy. In fact, Krittayaphong et al. demonstrated that the presence of MRI abnormalities in patients with RVOT arrhythmias submitted to catheter ablation, without diagnostic criteria for ARVC, was associated with a higher recurrence rate [5]. Those findings could be an indicator of an abnormal anatomical substrate originating the PVCs.

Recently it has been proved that in Brugada syndrome, initially considered a purely electrical disease, patients have lower left and right longitudinal strain and more heterogeneous contractions than healthy controls, irrespective of the presence of previous events [19]. We can then say that the fact we haven’t previously found imaging abnormalities doesn’t necessarily mean there are no pathological findings associated with these conditions.

As study limitations, we note that our conclusions were based on a single center study, with a relatively small number of patients. The study and the control group were only matched for age and gender and that could have induced bias, although we believe that was not the case because both groups did not differ significantly in relation to cardiovascular risk factors. Besides, we cannot truly determine if the strain abnormalities were a precursor or an effect of RVOT PVCs. It would have been interesting to have a baseline study before the development of the PVCs and to assess the long-term outcome of the patients and the correlation with the imaging abnormalities found.

In conclusion, this group of RVOT PVCs patients with structurally apparent normal hearts, had worse RV longitudinal strain values (and therefore sub-clinical myocardial dysfunction) than healthy controls. Therefore, we recommend a closer follow-up by serial echocardiographic imaging and cardiac MRI in cases of persistence of strain abnormalities.

Declaration of competing interest

Authors declare no Conflict of Interests for this article.

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