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Periodic repolarization dynamics in patients with moderate to severe aortic stenosis☆

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Abstract

Background: Periodic repolarization dynamics (PRD) refers to low-frequency oscillations of cardiac repolarization, most likely related to phasic sympathetic activation. Increased PRD is a validated predictor of mortality after myocardial infarction and in ischemic heart disease, but has not been tested in aortic valve stenosis (AS). Here, we assessed PRD in patients with AS and tested its correlation with clinical and hemodynamic parameters as well as markers of heart rate variability (HRV).

Materials and methods: We prospectively enrolled 139 consecutive patients with moderate to severe AS in sinus rhythm. In all patients we performed a 24-h Holter ECG in Frank–leads configuration. We assessed PRD according to previously published technologies from the nocturnal hours (0 am–6 am) and dichotomized PRD at the established cut-off value of ≥ 5.75 deg^2. In addition to clinical and hemodynamic markers, we also assessed deceleration capacity (DC) of heart rate, heart rate turbulence and standard HRV parameters.

Results: In the patients studied, PRD was 6.55 ± 3.96 deg^2. Seventy-three patients (52.5%) had increased PRD. Among them, 36 (49.9%) patients were classified as being asymptomatic. There was no association between increased PRD and clinical or hemodynamic markers, including presence of symptoms, NYHA-classification, aortic valve area, and left-ventricular ejection fraction. Thirty-three of the 73 (45.2%) patients with PRD ≥ 5.75 deg^2 also suffered from decreased vagal tonic activity by means of abnormal DC (≤ 2.5 ms) indicating severe autonomic dysfunction.

Conclusion: Prevalence of increased PRD is high among patients with moderate to severe AS. Patients with increased PRD cannot be identified by clinical or hemodynamic markers Future studies should test the prognostic value of PRD in patients with AS.

Keywords: Periodic repolarization dynamics; Sympathetic nervous system; Aortic stenosis

Introduction

Aortic valve stenosis (AS) is the most prevalent heart valve disorder and the third most common cardiovascular disease after coronary artery disease (CAD) and hypertension in developed countries [1]. The natural prognosis of AS varies widely, ranging from good to unfavorable. Therefore, accurate risk stratification is crucial for treatment decision. According to current guidelines an invasive treatment is delayed until development of symptoms or impairment of left-ventricular ejection fraction (LVEF) [2,3]. However, this "wait for symptoms" strategy might prove deleterious, as the symptomatic status cannot be reliably assessed especially in the elderly patients.

Increased sympathetic nervous system (SNS) activity is a sign of progression of the disease, which can be effectively reversed after trancatheter aortic valve replacement (TAVR) [4]. As AS worsens, cardiac output is reduced, and this situation leads to increased SNS activity, which finally predisposes to fatal cardiac arrhythmias and cardiac decompensation. As of yet, accurate assessment of SNS required an invasive approach using microneurographic measurements from the peroneal nerve [4].

Recently, we proposed a novel approach to non-invasively assess the effect of SNS-activity on the heart that substantially differs from previous methods [5]. So-called "Periodic Repolarization Dynamics (PRD)" evaluates sympathetic-activity-associated low-frequency periodic changes of cardiac repolarization and opens new perspectives for identifying

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high-risk patients, which cannot be identified by other methods. PRD has been shown to be an important predictor of mortality and cardiovascular mortality in patients with acute [5] and chronic myocardial infarction (MI) [6]. Therefore, the aim of the present study is to evaluate PRD in patients with moderate to severe AS and to test its association with clinical and hemodynamic parameters, as well as markers of HRV. The present study is a substudy of the Risk Prediction in Aortic Stenosis study (PREDICT-AS; ClinicalTrials.gov number NCT01422044).

Material and methods

Study population

Between September 2009 to November 2012 we prospectively enrolled patients who presented for evaluation of known or suspected AS at the Eberhard-Karls-University of Tuebingen, Germany (Fig. 1). Eligible patients were in sinus rhythm and had moderate to severe AS (aortic valve area [AVA] ≤ 1.5 cm^2 and/or mean aortic pressure gradient ≥ 25 mm Hg), which was confirmed invasively or by echocardiography. Patients were excluded if they were not in sinus rhythm, if they had an acute coronary syndrome or significant coronary stenosis requiring revascularization, or when an additional hemodynamically significant valve lesion was present. In this post-hoc analysis we also excluded patients for whom a Holter ECG in Frank leads configuration was either not available or did not meet the standards for PRD assessment.

Assessment of periodic repolarization dynamics

In all patients, 24-h Holter recordings (Cardio CM 3000, Getemed, Teltow, Germany) were performed in Frank leads configuration at a sample rate of 256 Hz. As long as PRD assessment requires standardized conditions in supine, resting position, we only used the nocturnal phase between 00 a.m. to 06 a.m. for evaluation of PRD. The technical details of PRD assessment have been described elsewhere [5]. Briefly, X-,Y- and Z–leads are converted to a set of polar coordinates defined by two angles (azimuth and elevation) and the amplitude Amp. We used established algorithms in order to define the beginning and ending of each T-wave [7]. In a second step, we integrated the spatiotemporal characteristics of each T-wave into a single vector $T°$, which is defined by the so-called weight-averaged azimuth (WAA) and weight-averaged elevation (WAE):

$$Weight\ Averaged\ Azimuth\ (WAA) = \frac{\sum_{t=T_{start}}^{t=T_{end}} (Amp_t * \ Azimuth_t)}{\sum_{t=T_{start}}^{t=T_{end}} (Amp_t)} \quad (1)$$

$$Weight\ Averaged\ Elevation\ (WAE) = \frac{\sum_{t=T_{start}}^{t=T_{end}} (Amp_t * \ Elevation_t)}{\sum_{t=T_{start}}^{t=T_{end}} (Amp_t)} \quad (2)$$

In a third step, we estimated the instantaneous degree of repolarization instability by means of the angle $dT°$ between successive repolarization vectors. $dT°$ was calculated using

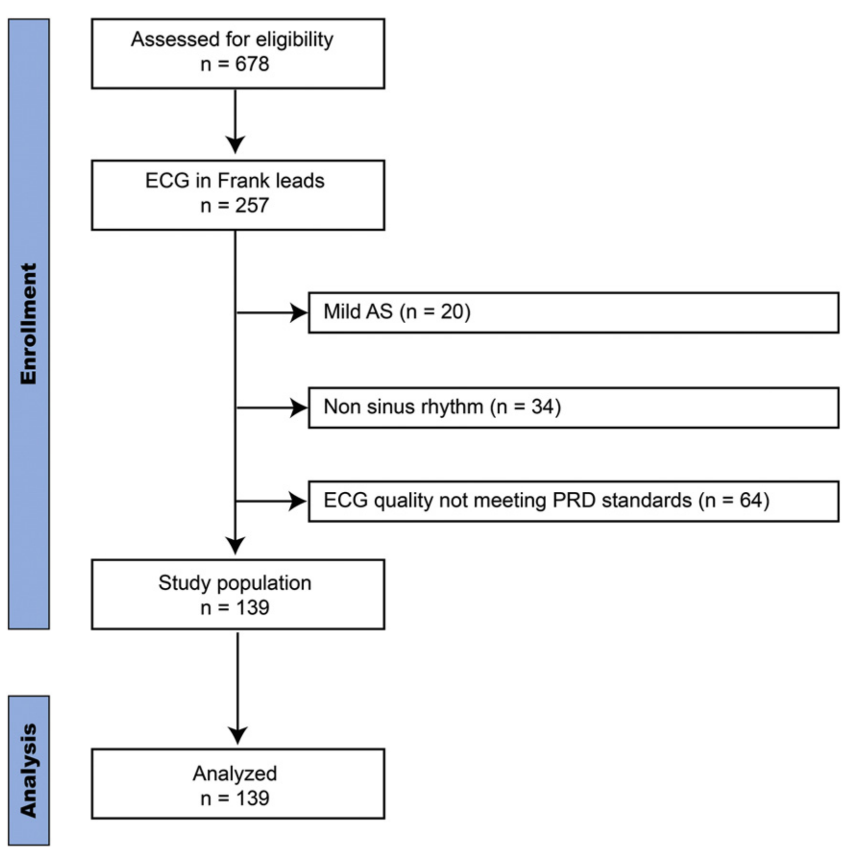

Fig. 1. Consort flow-diagram for patient selection. AS = aortic stenosis.