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Severe autonomic failure as a predictor of mortality in aortic valve stenosis

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ABSTRACT

Background: Identification of new risk markers in aortic valve stenosis (AS) is of great interest. Here, we hypothesized that the presence of severe autonomic failure (SAF) is an important prognostic marker in both, symptomatic patients undergoing invasive treatment for severe AS, and in asymptomatic patients with severe AS who were primarily treated conservatively.
Methods: We prospectively enrolled 300 patients with severe AS (aortic valve area <1.0 cm^2 or mean aortic gradient >40 mm Hg) in sinus rhythm. All patients underwent a 24-h Holter recording for assessment of heart rate turbulence (HRT) and deceleration capacity (DC). Patients with both, abnormal DC and HRT were considered to suffer from SAF.
Results: The first hypothesis was tested in 216 symptomatic patients who underwent successful aortic valve replacement (AVR) or transcatheter aortic valve implantation (TAVI). During follow-up of 2 years, 29 of these patients died. SAF was the strongest independent predictor of mortality (hazard ratio 5.6, 95% confidence interval 2.6–12.0; $p < 0.001$) with 2-year mortality rates of 50.0% and 10.7% in SAF-positive and SAF-negative patients, respectively ($p < 0.001$). The second hypothesis was tested in 71 patients, who were asymptomatic at study entry and for whom a primarily conservative treatment strategy was proposed. During follow-up, 10 of these patients died. SAF also predicted death in asymptomatic patients with 2-year mortality rates of 52.4% and 8.7% in SAF-positive and SAF-negative patients, respectively ($p = 0.010$).
Conclusions: SAF is a strong and independent predictor of mortality in symptomatic and asymptomatic patients with severe AS.

1. Introduction

Aortic valve stenosis (AS) is the most common type of valvular heart disease in the industrialized world and affects up to 7% of the general population age 65 years and over [1,2]. The natural prognosis of AS varies widely, ranging from rather favorable to deleterious. Therefore, accurate risk assessment is crucial for the selection of the best treatment strategy in the individual patient. According to current guidelines, invasive treatment of severe AS is usually delayed until symptoms occur [3–5]. However, this "wait for symptoms" strategy can be dangerous, as the symptomatic status cannot be reliably assessed in many patients. Hence, novel markers that allow for objective and unbiased estimation of patient risk are of great general interest.

Assessment of cardiac autonomic function provides important insights into the regulatory properties of the cardiovascular system. Markers of cardiac autonomic dysfunction are strong predictors of mortality in post-infarction [6] and heart failure patients [7], yielding independent prognostic information from left ventricular ejection fraction (LVEF) and NYHA class. Alterations of cardiac autonomic function have also been reported in AS [8] but their prognostic meaning is largely unknown.

Here, we hypothesized that cardiac autonomic dysfunction is an important prognostic marker in patients with severe AS. We used a combination of two established Holter-based risk predictors to assess autonomic function. Heart rate turbulence (HRT) [9] quantifies the baroreflex-mediated short-term oscillation of the heart rate following ventricular premature complexes (VPCs). Deceleration capacity (DC) [10] is considered to be representative of tonic vagal activity. Combined abnormalities of HRT and DC have been defined as "severe cardiac autonomic failure" (SAF) [6] and have shown to indicate poor prognosis in post-infarction patients [6]. We tested two different hypotheses: SAF

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predicts mortality in (1) symptomatic patients undergoing invasive treatment for severe AS, as well as in (2) asymptomatic patients with severe AS who were primarily treated conservatively at study entry.

2. Methods

2.1. Recruitment and follow-up

We prospectively studied consecutive patients with severe AS who were referred from September 2009 to November 2012 for evaluation of therapeutic options at a tertiary university center. Patients were included if aortic valve area (AVA) was <1.0 cm^2, mean aortic gradient was >40 mm Hg or jet velocity was >4.0 m/s, confirmed either invasively or by echocardiography. Patients were excluded if they were not in sinus rhythm, if they had an acute coronary syndrome or significant coronary artery stenosis requiring revascularization <4 weeks, if an additional significant valve lesion was present or if the patient's life expectancy was assumed to be less than one year because of non-cardiac diseases.

Therapeutic options for every patient were discussed at a weekly interdisciplinary conference of cardiologists and cardiac surgeons, who were not involved in the study. All recommendations (medical treatment, aortic valve replacement (AVR), transcatheter aortic valve implantation (TAVI)) were based on current guidelines [3–5]. The local ethics committee approved the study. Every patient gave written informed consent.

2.2. Assessment of severe autonomic failure

At enrollment, all patients underwent 24-h Holter recordings (Cardio CM 3000, Getemed, Teltow, Germany) for assessment of HRT and DC. An experienced technician blinded to the patient's clinical status manually reviewed and processed all recordings using standard commercial equipment (CardioDay, Getemed, Teltow, Germany) to obtain the sequence of individual R–R intervals together with beat classification (sinus beat, VPC, artifact).

HRT and DC were calculated according to previously published technologies using established cut-off values by use of customized and validated software [9–11]. Briefly, HRT quantifies the baroreflex-mediated short-term oscillation of the cycle lengths following ventricular premature complexes [9]. The oscillation is composed of an initial acceleration of heart rate followed by a gradual deceleration of heart rate. The two phases of HRT are quantified by two numerical parameters, turbulence onset and turbulence slope. Turbulence onset is calculated as:

$$TO = \frac{(RR_1 + RR_2) - (RR_{-2} + RR_{-1})}{(RR_{-2} + RR_{-1})} \times 100 \ [\%]$$

where RR_{-2} and RR_{-1} are the two RR intervals immediately preceding the VPC coupling interval, and RR_1 and RR_2 are two RR intervals immediately following the compensatory pause [11]. Turbulence slope is defined as the maximum positive regression slope assessed over any 5 consecutive sinus rhythm R–R intervals within the first 15 sinus rhythm RR intervals after the VPC [11]. Hence, in normal subjects, the initial brief acceleration of sinus rate after the VPC is characterized by negative TO, and the subsequent rate deceleration is characterized by positive TS.

DC quantifies the mean amplitude of all deceleration-related oscillations of heart rate observed in the recording period [10]. Assessment of DC is based on a new signal processing algorithm termed phase-rectified signal averaging (PRSA) which is capable of extracting periodic components out of non-stationary, noisy signals [12]. Briefly, the technique consists of five steps. In the first step, RR intervals are identified which are longer than their preceding intervals. In order to exclude artifacts, RR-intervals that are longer than 105% of the preceding RR-interval are excluded. These RR-intervals are called anchors. In the second step, segments around anchors are defined. Please note that segments surrounding adjacent anchors may overlap. In the third and fourth steps, segments are aligned at the anchors and subsequently averaged. The so-called PRSA-signal is quantified by Haar-wavelet analysis [10]:

$$DC = {}^{1}\!/_{4} \times (x_0 + x_1 - x_{-1} - x_{-2})$$

where x_0 and x_1 are the averages of the anchors and the following RR-intervals, while x_{-1} and x_{-2} are the averages of the two RR-intervals preceding the anchors.

In line with previous investigations, patients with combined abnormalities of HRT (turbulence onset ≥0% and turbulence slope ≤2.5 ms/RR interval) and DC (≤4.5 ms) were considered to have SAF [6,13].

2.3. Conventional risk predictors

In all patients, peak and mean aortic gradient, AVA, and LVEF were assessed. In patients who underwent left and right heart catheterization, hemodynamic variables were obtained invasively, as follows: LVEF obtained by the area-length method from a single-plane right anterior oblique projection [14] and AVA calculated using the Gorlin formula [15]. In patients in whom no catheterization was performed, hemodynamic variables were obtained by echocardiography (iE33, Philips Medical Systems). In these patients, LVEF was assessed by the modified Simpson rule with images obtained from apical 4- and 2-chamber views. AVA was estimated by the continuity equation using the velocity–time integral of the aortic and left ventricular outflow tract flows.

The presence of chronic obstructive pulmonary disease (COPD) was defined by long term use of bronchodilators or steroids for lung disease. Extracardiac arteriopathy was considered present if the patient suffered from claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta, limb arteries or carotids. Neurological dysfunction was defined as a neurological disease severely affecting ambulation or day-to-day functioning. Renal insufficiency was considered present if serum creatinine was >200 μmol/l. Systolic pulmonary artery pressure (PAP_{sys}) was assessed by continuous wave Doppler echocardiography based on tricuspid pressure gradient by adding mean right arterial pressure estimated from inferior vena cava diameter and motion during respiration. The presence of pulmonary hypertension was considered present if PAP_{sys} was >60 mm Hg. Based on these and other risk factors, the logistic EuroSCORE was calculated as previously described [16].

Brain natriuretic peptide (BNP) levels were assessed by immunoassay at study enrollment (ADVIA Centaur® BNP assay, Siemens Healthcare Diagnostics). In 88 patients, N-terminal proBNP (Nt-proBNP) was assessed instead of BNP (Immulite 2000, Siemens Healthcare Diagnostics) because of a change in hospital laboratory standards. In 59 symptomatic and 35 asymptomatic patients, neither BNP nor Nt-proBNP levels were available. BNP and Nt-proBNP were dichotomized at 550 pg/ml [17] and 4691 pg/ml [18], respectively. Patients with BNP ≥550 pg/ml or Nt-proBNP ≥4691 pmol/l were classified as being BNP positive.

2.4. Study endpoints

The primary endpoint was total mortality within the first 2 years of follow-up; the secondary endpoints were cardiac mortality as well as the composite of cardiac mortality and hospitalization resulting from decompensated heart failure within the first 2 years of follow-up. If a patient died during follow-up, the cause of death was verified from hospital and autopsy records and from either the primary physician or those witnessing the death. An independent endpoint committee adjudicated the mode of death. Deaths were categorized as cardiac and non-cardiac. Patients who were asymptomatic at study entry but underwent AVR or TAVI during follow-up were censored at the date of invasive treatment.

2.5. Statistical analysis

Continuous variables are presented as median and IQR and were compared using the Mann–Whitney U test. Qualitative data are expressed as percentages and were analyzed using the chi-square test. The relations of risk variables to the primary and secondary endpoints were investigated with the use of Cox proportional-hazards models. The proportional hazard assumption of the various parameters was investigated by using Schoenfeld residuals. Multivariable Cox regression analysis was adjusted for age and gender. Continuous variables were dichotomized at the median. Mortality rates were estimated by the Kaplan–Meier method. Hazard ratios (HRs) are presented with 95% confidence intervals (CIs). Differences were considered statistically significant if $p < 0.05$. Statistical analyses were performed using SPSS 20.0.

3. Results

During recruitment period, 678 patients presented for evaluation of AS. 300 patients fulfilled the inclusion criteria. Of these, 229 and 71 patients were classified as being symptomatic and asymptomatic, respectively (Fig. 1).

3.1. Prognostic value of SAF in symptomatic patients undergoing AVR or TAVI

The first hypothesis was tested in 216 of the 300 patients, who were classified as being symptomatic at study entry and who underwent successful AVR (n = 61) or TAVI (n = 155) 16 (median, IQR 3–48) days after enrollment. Patients were aged 79 (73–84) years and 110 (50.5%) were women. AVA was 0.7 (0.5–0.8) cm^2 and LVEF was 55 (45–60) (Table 1). 32 of the 216 patients (14.8%) were SAF-positive. During a median follow-up of 450 (IQR 184–739) days, 29 patients (13.4%) died.

SAF was highly significantly associated with the primary endpoint. The 32 SAF-positive patients had a cumulative 2-year mortality rate of 50.0% compared to 10.7% in the 184 SAF-negative patients ($p < 0.001$; Table 2, Fig. 2A). SAF was also highly significantly associated with the secondary endpoints including cardiac deaths and the composite of cardiac deaths and heart failure-related hospitalizations (Table 2, Fig. 2B). Multivariable analysis revealed that SAF was the strongest predictor of mortality (hazard ratio of 5.6, 95% CI 2.6–12.0; $p < 0.001$) which was independent of elevated serum levels of BNP (hazard ratio of 2.7, 95% CI 1.2–5.9; $p = 0.013$) and other risk factors (Table 3).