International Journal of Cardiology 180 (2015) 122–128

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Resting heart rate and risk of adverse cardiovascular outcomes in asymptomatic aortic stenosis: The SEAS study

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ARTICLE INFO

Article history:
Received 23 September 2014
Received in revised form 7 November 2014
Accepted 23 November 2014
Available online 26 November 2014

Keywords:
Aortic valve stenosis
Resting heart rate
Risk stratification

ABSTRACT

Background: An elevated resting heart rate (RHR) may be an early sign of cardiac failure, but its prognostic value during watchful waiting in asymptomatic aortic stenosis (AS) is largely unknown.
Methods: RHR was determined by annual ECGs in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study of asymptomatic mild-to-moderate AS patients. Primary endpoint in this substudy was major cardiovascular events (MCEs) and secondary outcomes its individual components. Multivariable Cox-models using serially-measured RHR were used to examine the prognostic impact of RHR per se.
Results: 1563 patients were followed for a mean of 4.3 years (6751 patient-years of follow-up), 553 (35%) MCEs occurred, 10% (n = 151) died, including 75 cardiovascular deaths. In multivariable analysis, baseline RHR was independently associated with MCEs (HR 1.1 per 10 min^{-1} faster, 95% CI: 1.0–1.3) and cardiovascular mortality (HR 1.3 per 10 min^{-1} faster, 95% CI: 1.0–1.7, both $p \leq 0.03$). Updating RHR with annual in-study reexaminations, time-varying RHR was highly associated with excess MCEs (HR 1.1 per 10 min^{-1} faster, 95% CI: 1.1–1.3) and cardiovascular mortality (HR 1.4 per 10 min^{-1} faster, 95% CI: 1.2–1.7, both $p \leq 0.006$). The association of RHR with MCEs and cardiovascular mortality was not dependent on atrial fibrillation status (both $p \geq 0.06$ for interaction).
Conclusions: RHR is independently associated with MCEs and cardiovascular death in asymptomatic AS (Clinicaltrials.gov; unique identifier NCT00092677).

1. Introduction

A resting heart rate (RHR) of 60–80 beats min^{-1} is considered normal in healthy adults, and is mainly determined by vagal tone [1]. Although RHR is largely a nonspecific marker of underlying pathology, numerous observational studies have related an increased RHR to adverse outcomes in populations with and without established cardiovascular disease [2–6], including patients with increased afterload due to hypertensive heart disease [7–9]. However, even though previous studies suggest that autonomic control of RHR is impaired in patients with aortic stenosis (AS) [10–12], and possibly regained following aortic valve replacement (AVR) [13,14], there are very limited data on the prognostic impact of RHR in this patient population [15]. In the present study, we hypothesized that an increased RHR is an early marker of cardiac failure, and that RHR therefore contains prognostic information on adverse outcomes in patients with asymptomatic AS. The primary aim of this study was therefore to examine if RHR, as determined by resting 12-lead ECGs at baseline, and by annual reexaminations, was independently related to clinical endpoints, and occurrence of cardiovascular or all-cause mortality, during long-term follow-up in initially asymptomatic patients with mild to moderate AS and preserved left ventricular (LV) systolic function. A secondary aim was to investigate

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http://dx.doi.org/10.1016/j.ijcard.2014.11.181
0167-5273/

the cross-sectional relations of RHR in a large contemporary population of asymptomatic AS.

2. Methods

2.1. Study population

The Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study was a multicenter, randomized, double-blind, placebo-controlled study, investigating whether intensive lipid lowering with simvastatin/ezetimibe combination vs. placebo could reduce the need for AVR and risk of cardiovascular morbidity and mortality in 1873 patients, aged 45 to 85 years, with asymptomatic mild-to-moderate AS (defined as echocardiographic aortic valve thickening accompanied by Doppler-measured aortic peak flow velocity ≥2.5 and ≤4.0 m/s and normal systolic LV function). The main outcomes including study design, organization, clinical measures, exclusion criteria (most important systolic heart failure, diabetes and clinically apparent cardiovascular atherosclerosis), baseline characteristics and main outcome have been published previously [16,17]. All SEAS patients were automatically enrolled in the SEAS ECG substudy. This study uses post-hoc analysis of SEAS ECG data to examine the association of RHR with major cardiovascular events (MCEs) during prospective follow-up of initially asymptomatic patients with mild to moderate AS. The SEAS study is registered with Clinicaltrials.gov; unique identifier: NCT00092677. We adhere to the statement of ethical publishing as appeared in the International Journal of Cardiology.

2.2. Resting heart rate

RHRs were determined by resting 12-lead ECGs obtained at baseline and at annual in-study visits. ECG study protocol, reading procedures and reproducibility have been published [18]. In brief, ECGs were recorded annually at local study centers, and sent to the central ECG core laboratory at The Heart Center, Rigshospitalet, Copenhagen, Denmark. For patients in sinus rhythm, RHR was estimated by averaging RR intervals over three adjacent beats. If atrial fibrillation was detected, RHR was averaged as number of beats over a 10 s recording.

2.3. Echocardiography

Echocardiographic study protocol, reading procedures and reproducibility have been published [19]. In short, transthoracic echocardiograms were read by an expert blinded to randomization and study visit at the SEAS echocardiography core laboratory, located at Haukeland University Hospital in Bergen, Norway. Aortic valve area was calculated applying the continuity equation, in accordance with recommendations [20], and averaged over ten consecutive beats in patients with atrial fibrillation. Stroke volume was measured using the Teichholz correction of the cube formula and indexed to body surface area (SVi) and height to the power of 2.04. LV dimensions and wall thicknesses were measured on two-dimensional images following the American Society of Echocardiography guidelines, using an anatomically validated formula [21]. Left atrial volume was measured in LV end-systole and end-diastole by the modified Simpson's monoplane method in the apical 4-chamber view and indexed by body surface area [22]. Mitral regurgitation was assessed by color Doppler using previously described 4-point grading scale; grade ≥2 corresponding to a moderate to severe mitral regurgitation [23].

2.4. Left ventricular systolic properties and afterload

Midwall shortening was used as the primary measure of myocardial contractility. LV ejection fraction was measured by the biplane method of disks [24]. The composite impact of arterial and valvular (Zva) afterload was approximated as: Zva = mean aortic gradient + systolic blood pressure (BP) / SVi. Individual components of arterial LV afterload were calculated as: (1) systemic arterial compliance = SVi / (systolic BP − diastolic BP); and (2) total peripheral resistance = 80 × mean BP / cardiac output. Myocardial oxygen consumption was calculated as: wall stress-mass-heart rate product = circumferential end-systolic-stress × LV mass × heart rate ($g \times kdyne/cm^2 \times bpm \times 10^6$).

2.5. Endpoints

All endpoints in the main study were classified by an endpoint classification committee blinded to randomization according to a prespecified endpoint manual outlined by the SEAS Steering Committee [16]. The primary endpoint in this substudy was MCEs, a composite of the first of death from cardiovascular causes, aortic valve replacement, congestive heart failure as a result of AS progression, myocardial infarction, hospitalization for unstable angina, coronary artery-bypass grafting, percutaneous coronary intervention, or nonhemorrhagic stroke [16,17]. The composite endpoint included both AS-related and ischemic events to account for possible cardiovascular symptoms and events occurring in patients with AS. Secondary outcomes were the individual components of the composite endpoint.

2.6. Statistical analysis

Data were analyzed using the Statistical Analytical Software version 9.2 (SAS, Cary, NC). Continuous data are expressed as mean ± SD and categorical variables as proportions. Based on published literature [1,25], cutoffs of <60 min^{-1}, 60–80 min^{-1}, and ≥80 min^{-1} were used as partitions for RHR. Comparisons of continuous variables were evaluated by two-way ANOVA and the Wilcoxon test as appropriate. Trend tests were used for categorical data. Pairwise comparisons with RHR < 60 min^{-1} were Bonferroni corrected for multiple comparisons. Linear regression analysis was used to examine the cross-sectional correlates of RHR as a continuous variable with ECG, echocardiographic, and clinical parameters. A paired t-test was used to evaluate changes in RHR from last measurement before AVR to the first scheduled in-study reexamination after AVR. Correlates of RHR, as a continuous and categorical variable (<60 min^{-1}, 60–80 min^{-1}, and ≥80 min^{-1}), with of rates primary and secondary endpoints were analyzed by Cox time-to-event analyses. Event rate ratios are presented as hazard ratios (HR) with 95% confidence intervals (CI). Multivariable associations were evaluated by adjusting the Cox-models for covariates associated with an increased RHR at baseline in addition to variables that have previously been shown to predict adverse outcome in the SEAS population (age, sex, mean aortic gradient, LV stroke volume indexed to body surface area, Voltage in $R_{V5-6} + S_{V1}$, white blood cell count, P-wave neg. amplitude lead-V_1, LV ejection fraction, LV mass indexed to body surface area, body mass index, and hypertension). Beta-blocker therapy at baseline was a forced covariate in all analyses. To avoid collinear information, variables that included RHR in their own calculation, e.g. myocardial oxygen consumption, were not included in the multivariable Cox models. The Andersen–Gill formulation of the Cox-model was used to evaluate the predictive values of time-varying RHR [26]. Cumulative martingale residuals were used to assess proportional hazard and linear assumption (p-values for the lack of linear relation and proportional hazard for RHR with respect to CV death were 0.85 and 0.50, respectively). Two tests of interaction were performed; 1) between resting heart rate as a continuous variable and atrial fibrillation on the relation to MCEs and cardiovascular death; and 2) between resting heart rate and time-varying AVR on the relation to post-AVR survival. For all hypothesis testing a two-tailed $p < 0.05$ was required for statistical significance.

3. Results

3.1. Baseline characteristics

Baseline ECGs were available in 1563 patients (83%); there was no detectable difference in age, mean aortic gradient, LV ejection fraction or the percentage of women among subjects with and without available baseline ECGs (all $p > 0.26$). At the time of inclusion, increased RHR, as a group variable (≥80 min^{-1}), was associated with more severe AS, impaired systolic function, atrial fibrillation, more negative P-wave amplitude in ECG lead V_1, lower ECG LV hypertrophy by Sokolow–Lyon voltage, reduced kidney function, and a higher total white blood cell count (Table 1). Analyzing RHR as a continuous variable, female gender, greater mean aortic gradient, reduced SVi, atrial fibrillation, lower Cornell voltage–duration product, and higher total white blood cell count emerged as the strongest predictors of faster RHR, although they only explained a small part of the variance in RHR (all $p < 0.001$ for regression coefficients in a multivariable generalized linear model with $R^2 = 0.11$).

3.2. Prognostic impact of baseline resting heart rate

During the course of the study, 450 (29%) patients were referred for AVR, 75 (5%) suffered cardiovascular death, 151 (10%) died, and 553 (35.4%) composite events occurred. Proportion of subjects meeting endpoints according to baseline partitions of RHR is given in Table 2 and Supplemental Table 1. In univariate comparisons, increased RHR, as continuous or discrete variable (Fig. 1), was associated with a clear excess in the risk of MCEs (Table 3). Importantly, even when adjusting by other important risk factors, RHR as a continuous variable remained associated with increased risk of MCEs (Table 3). Secondary outcome analyses confirmed the association of RHR (Fig. 2) with adverse outcome (Table 4). Categorization of RHR seemed to mitigate some of the risk associated with RHR as a linear predictor. As such, when adjusting RHR by other risk factors, only higher RHR as continuous variable remained a strong and independent predictor of MCEs and cardiovascular deaths (Tables 3 and 4, respectively). There was no detectable interaction between RHR and atrial fibrillation, as assessed on the baseline ECG, on the risk of MCEs or cardiovascular death (all $p \geq 0.06$).

3.3. Prognostic impact of time-varying resting heart rate

Including information on in-study RHR obtained from the annual in-study visits, resulted in nearly equal univariate associations with