Resting heart rate and risk of sudden cardiac death in the general population: Influence of left ventricular systolic dysfunction and heart rate-modulating drugs

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BACKGROUND Higher levels of resting heart rate (HR) have been associated with sudden cardiac death (SCD) but mechanisms are poorly understood. We hypothesized that severe left ventricular systolic dysfunction (LVSD) and HR-modulating drugs explain the HR-SCD relationship.

OBJECTIVE To evaluate the relationship between HR, severe LVSD, HR-modulating drugs, and SCD in the community by using a case-control approach.

METHODS From the ongoing Oregon Sudden Unexpected Death Study, SCD cases (n = 378) aged ≥35 years and with electrocardiogram-documented resting HR were compared to 378 age- and gender-matched control subjects with coronary artery disease (mean age 68 ± 13 years; 69% man). Associations with SCD were assessed by using multivariable logistic regression.

RESULTS Mean resting HR was significantly higher among SCD cases compared to controls (7.5 beats/min difference; $P < .0001$). HR was a significant determinant of SCD after adjustment for significant comorbidities and medications (odds ratio for 10 beats/min increase 1.26; 95% confidence interval 1.14–1.38; $P < .0001$). After considering LVSD, resting HR was slightly attenuated but remained significantly associated with SCD ($P = .005$). In addition to diabetes and digoxin as well as pulmonary and renal disease, LVSD was also independently associated with SCD (odds ratio 1.79; 95% confidence interval 1.11–2.87; $P = .02$).

CONCLUSIONS Contrary to expectations, the significant relationship between increased resting HR and SCD persisted even after adjustment for LVSD and HR-modulating drugs. These findings suggest a potential role for additional novel interventions/therapies that modulate autonomic tone.

KEYWORDS Cardiac arrest; Mortality; Beta-blockers; Heart failure; Case-control study; Medications

ABBREVIATIONS **CAD** = coronary artery disease; **CI** = confidence interval; **EKG** = electrocardiogram; **EMS** = emergency medical services; **HR** = heart rate; **LVSD** = left ventricular systolic dysfunction; **OR** = odds ratio; **SCD** = sudden cardiac death

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Introduction

Subjects with elevated resting heart rate (HR) have increased risk of overall cardiovascular mortality[1–3] as well as sudden cardiac death (SCD).[1,2,4,5] This well-established association was principally observed in large cohort studies, reporting mid- and long-term follow-up of healthy middle aged subjects, as well as studies carried out among specific selected populations. The importance of considering resting HR has been recently emphasized by the favorable effect of lowering HR among selected patients with elevated resting HR.[6]

However, the extent to which elevated resting HR is independently (beyond the adjustment for traditional cardiovascular risk factors) associated with SCD still remains unclear since many potential confounding factors exist. First, left ventricular systolic dysfunction (LVSD) may be significantly more prevalent in patients who suffer SCD and could also contribute to elevated HR in the population.[7,8] Second, beta-blockers are commonly used in coronary artery disease (CAD), a condition that has been frequently identified in subjects who suffered SCD, and are potential factors contributing to lower HR.[9,10] Finally, other HR-lowering drugs (such as calcium channel blockers or digoxin) are commonly used in clinical practice, mainly in the treatment of systemic hypertension and atrial fibrillation, whereas beta2-agonists (drugs that increase HR) are usually given for lung disease. Taken together, the

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potential relationship between resting HR and SCD appears particularly complex and the setting of the general population as well as the presence of influencing factors (such as LVSD and HR-modulating drugs) are important considerations.

We, therefore, evaluated the potential effect of HR-modulating drugs and severe LVSD on the HR-SCD relationship by using a large case-control approach in the general population.

Methods

The Oregon Sudden Unexpected Death Study

The ongoing Oregon Sudden Unexpected Death Study prospectively identifies out-of-hospital SCD occurring among residents of the Portland, OR, metropolitan region (population approximately 1,000,000).[11–14] The majority of cases are identified through the region's emergency medical services (EMS) system, a 2-tier, advanced life support system provided by fire and ambulance paramedics, as well as Medical Examiner's office. Information regarding the circumstances of SCD, patients' characteristics, and comorbidities were determined from EMS records, hospital medical records, as well as information from the pathology department and death certificates. This study was approved by the Institutional Review Boards of Cedars-Sinai Medical Center, Oregon Health and Science University, as well as other participating hospitals.

Definition of SCD cases and controls

SCD was defined as a sudden unexpected pulseless condition occurring within 1 hour of symptom onset; if unwitnessed, subjects were required to be seen alive and symptom-free within 24 hours of their sudden arrest.[15] After review of first responder reports, autopsy, and medical records as well as a process of in-house adjudication by 3 physicians, SCD cases were enrolled in the study. Patients with terminal illness and known noncardiac causes (eg, trauma, overdose, pulmonary embolism, cerebrovascular accident, and terminal illness such as cancer) were excluded.

Since at least 80% of SCD occurs in the setting of existing CAD,[16,17] control subjects were selected to include individuals who were alive with documented chronic as well as acute CAD enrolled from 3 sources: clinics of participating health systems, individuals receiving a coronary angiogram, or patients transported by the EMS for complaints suggestive of ongoing coronary ischemia. Controls were selected from the same geographical area during the same time period as the cases. This study design allows for the investigation of factors related to SCD risk while controlling for CAD. CAD was defined as history of myocardial infarction, coronary revascularization, or at least 50% stenosis on coronary angiography or autopsy.

Eligibility of study participants for the present analysis

In the present analysis, we considered SCD cases aged ≥35 years with previous electrocardiogram (EKG) documentation of HR (closest EKG prior and unrelated to the cardiac arrest was used: median 12.5 [interquartile range 2.0–32.1] months prior to SCD). EKG tracings were obtained from the existing medical records from clinic or hospital visits unrelated to the study. For control subjects (age ≥35 years) without a preascertainment EKG, we used an EKG obtained at a 1-time study visit. Resting HR was evaluated from the standard 12-lead EKG (paper speed 25 mm/s; amplitude 10 mm/mV) in sinus rhythm. Cases and controls were frequency matched by age (using 5-year categories), sex, and presence of CAD.

Information on the history of medical disorders and medication use was obtained from medical records (median 1.3 [interquartile range 0.01–9.3] months prior to SCD). Clinical characteristics included in this analysis were body mass index, smoking, history of diabetes mellitus, hypo- and hyperthyroidism, hypertension, chronic obstructive pulmonary disease, asthma, chronic renal insufficiency, liver disease, use of beta-blocker, diltiazem, verapamil, digoxin, and beta2-agonist. Left ventricular systolic function was assessed by left ventricular ejection fraction from echocardiogram, angiogram, or multigated acquisition scan. Severe LVSD was defined as ejection fraction ≤35%.

Statistical analysis

In this frequency-matching study, unpaired univariate and multivariable statistical analyses were conducted. Independent samples t tests and Pearson χ^2 tests were used for case-control comparisons of continuous and categorical variables, respectively. HR was analyzed as a continuous as well as categorical variable using 10 or 20 beats/min categories. Multiple logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for SCD. The first model considered HR adjusted for clinical characteristics and medications that could influence the HR and were significant ($P \leq .05$) in the univariate analysis. The second model considered additional LVSD adjustment (severe dysfunction vs mild-moderate dysfunction or normal function). SAS 9.2 (SAS Institute Inc, Cary, NC) statistical software was used for analysis. Values are presented as n (%) or mean ± SD, and P value ≤.05 was considered significant for all analyses.

Results

Characteristics of SCD cases and controls

Between February 2002 and January 2012, 756 subjects (378 SCD cases and 378 matched controls) were eligible for the present analysis (mean age 67.7 ± 12.8 years; 69% men).

Characteristics of SCD cases and controls are summarized in Table 1. Overall, mean resting HR was 7.5 beats/min higher in cases (76.2 ± 17.4 beats/min) compared to controls (68.7 ± 16.3 beats/min; $P < .0001$). Controls were more likely to have HR under 60 or 60–69 beats/min, and cases were more likely to be in the higher HR categories ($P < .0001$; Figure 1). Although SCD cases were more likely to have history of diabetes than controls ($P = .0003$), there were no significant differences in other cardiovascular risk factors ($P = .29$; Table 1) or smoking status ($P = .11$).

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