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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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Abstract

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 rate-modulating drugs explain the HR-SCD relationship.

Objective—We evaluated the relationship between HR, severe LVSD, rate-affecting medications and SCD in the community, using a case-control approach.

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

Results—Mean resting HR was significantly higher among SCD cases compared to controls (7.5bpm difference, $p<0.0001$). Heart rate was a significant determinant of SCD after adjustment for significant co-morbidities and medications [OR for 10 bpm increase = 1.26; 95% CI (1.14 – 1.38); $p<0.0001$]. After considering LVSD, resting HR was slightly attenuated but remained significantly associated with SCD ($p=0.005$). In addition to diabetes, and digoxin as well as pulmonary and renal disease, LVSD was also independently associated with SCD (OR 1.79, 95% CI 1.11–2.87, $p=0.02$).

Conclusion—Contrary to expectations, the significant relationship between increased resting HR and SCD persisted even after adjustment for LVSD and rate-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

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Introduction

Subjects with elevated resting 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 age 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 are usually given for lung disease. Taken together, the 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 rate-modulating drugs) are important considerations.

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

Methods

The Oregon Sudden Unexpected Death Study (Oregon SUDS)

The ongoing Oregon SUDS prospectively identifies out-of-hospital SCD occurring among residents of the Portland, Oregon 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 two-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 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 one hour of symptom onset; if un-witnessed, 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, and a process of in-house adjudication by three physicians, SCD cases were enrolled in the study. Patients with terminal illness, known non-cardiac causes (e.g., 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 coronary artery disease (CAD), enrolled from three 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 age 35 years and older with previous EKG documentation of HR (closest EKG prior and unrelated to the cardiac arrest was used—median 12.5, IQR 2.0–32.1 months prior to SCD). EKG tracings were obtained from existing medical records from clinic or hospital visits unrelated to the study. For control subjects (age ≥ 35 years) without a pre-ascertainment EKG, we used an EKG obtained at a one-time study visit. Resting HR was evaluated from the standard 12-lead EKG (25-mm/s paper speed and 10-mm/mV amplitude) in sinus rhythm. Cases and controls were frequency matched by age (using 5 year categories), gender and presence of coronary artery disease.

Information on history of medical disorders and medication use was obtained from medical records (median 1.3, IQR 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 (COPD), asthma, chronic renal insufficiency, liver disease, use of beta-blocker, diltiazem, verapamil, digoxin and beta2-agonist. Left ventricular systolic function was assessed by LV ejection fraction (EF) from echocardiogram, angiogram or multi-gated acquisition scan. Severe LVSD was defined as EF < 35%.

Statistical Analysis

In this frequency-matching study, unpaired univariate and multivariable statistical analyses were conducted. Independent-samples *t*-tests and Pearson's chi-square 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 bpm categories. Multiple logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CI) for SCD. The first model considered HR adjusted for clinical characteristics and medications that could influence the HR and were significant ($p < 0.05$) 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 $\pm$ SD and p value < 0.05 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, 69.0% were male).

Characteristics of SCD cases and controls are summarized in Table 1. Overall, mean resting HR was 7.5 bpm higher in cases (76.2 ± 17.4 bpm) compared to controls (68.7 ± 16.3 bpm, $p < 0.0001$). Controls were more likely to have HR under 60 bpm, or 60–69 bpm, and cases more likely to be in the higher HR categories ($p < 0.0001$) (Figure 1). Although SCD cases were more likely to have history of diabetes than controls ($p = 0.0003$), there were no significant differences in other cardiovascular risk factors ($p = 0.29$, Table 1) or smoking

status ($p=0.11$). Pulmonary and renal diseases were also more common in case subjects ($p=0.0004$). Severe LVSD was more prevalent among SCD cases ($p=0.0001$).

The association of demographic variables and medications with HR is shown in Figure 2. Resting HR was significantly greater in cases compared to controls in nearly all subgroups examined. Overall, the case vs. control difference was 7.5 bpm. Irrespective of age, gender, beta-blocker use, and beta2 agonist use, the mean HR remained at least 7.1 bpm greater among cases than among controls ($p=0.002$). Although the difference in HR was highly significant in the absence of severe LVSD and among non-users of digoxin ($p<0.0001$), when severe LVSD was considered, there were no significant differences ($p=0.99$). As expected, subjects with severe LVSD had higher HR compared to non-LVSD subjects (78.7 ± 19.3 vs. 70.5 ± 16.1 bpm, $p<0.0001$).

Medication Use and Resting HR

Overall, beta2-agonist use was more prevalent in cases ($p=0.04$, Table 1). The use of digoxin was also more prevalent among SCD cases ($p<0.0001$). Other HR-affecting medications such as beta-blockers or calcium channel blockers were used in a similar proportion ($p=0.50$).

However, irrespective of beta-blocker or beta2-agonist use, resting HR in cases was 7–10 bpm higher compared to controls ($p=0.001$) (Figure 2). There was no significant difference between cases vs. controls in the HR of patients taking digoxin ($p=0.66$) (Figure 2). Overall, HR remained relatively stable across subgroups within cases and controls.

Heart Rate as a Determinant of SCD

In a logistic regression model adjusting for diabetes, pulmonary and renal disease, digoxin and beta2-agonists, a 10 bpm increase in HR increased odds of SCD by 26% [OR 1.26 (95%CI 1.14–1.38), $p<0.0001$]. Compared to a HR of 60–79 bpm, HRs of 80–99 bpm were significantly associated with increased risk of SCD [1.54(95%CI 1.04–2.29), $p=0.03$]. HR under 60 bpm was negatively associated with the risk of SCD [OR 0.47 (95%CI 0.31–0.70), $p=0.0002$].

A similar trend was found after adjustment for presence of severe LVSD. Higher HR and severe LVSD independently increased the odds of SCD (Table 2, Model II). In addition, HR remained a significant determinant of SCD among beta-blocker users [1.28(95%CI 1.13–1.45)] as well as among non-users [1.23(95%CI 1.05–1.43)] ($p=0.01$).

Discussion

In this case-control study conducted in the general population, we found that elevated resting HR was significantly associated with the occurrence of SCD. This association between resting HR and SCD remained robust after further adjustment for severe LVSD and HR affecting drugs (beta2-agonists and digoxin). Our findings draw attention to the existence of additional mechanisms affecting resting HR, the modulation of which could impact favorably on prevention of SCD.

In the Framingham Heart Study (subjects free of cardiovascular disease at entry into the study), increased HR was significantly associated with mortality from SCD (1). This association has also been reported in three other independent cohort studies of middle-aged white males (2,4,5). A positive association was also found in the Chicago studies (Chicago People's Gas Company, the Chicago Heart Association Detection Project in Industry and the Western Electric Company) among men free of ischemic heart disease (2). In the Paris Prospective Study, adjusted resting HR was a significant predictor of sudden death [RR 1.28

(95% CI 1.06–1.61)] among healthy, native Frenchmen 42–53 years of age employed by the Paris Civil Service (5). The British Regional Heart Study enrolled men aged 40–59 years with and without pre-existing ischemic heart disease (4). Men with no evidence of ischemic heart disease and HR of ≥ 90 bpm had five times higher risk of SCD compared to men with HR of <60 bpm. In men with pre-existing ischemic heart disease the risk of SCD was also increased with higher HR but somewhat attenuated. Our results, from the general population, are consistent with these earlier studies.

Although HR alters with age (18), it is affected by established CAD risk factors (hypertension, smoking, diabetes) (19), presence of severe LV dysfunction and particularly by several medications. Moreover, there are also known gender differences in resting HR (18). In our analysis elevated resting HR was associated with SCD independent of all of these factors. Beta-blockers are known to decrease the HR, cardiovascular mortality and SCD (9). We report that elevated HR was a determinant of SCD independent of beta-blocker use. Therefore, the effect of HR on mortality and SCD independent of beta-blocker use indicates that there may be room for other heart-rate lowering therapies. For example, Ivabradine, which inhibits the I_f current in the sino-atrial node of the heart, a mechanism that appears to be distinct from beta-blockers as well as other rate-affecting medications, has been recently tested in addition to beta-blocker therapy in the BEAUTIFUL Trial (morbidity-mortality Evaluation of the I_f inhibitor Ivabradine in patients with coronary disease and left ventricular dysfunction) (6,20). Reduction in HR by Ivabradine resulted in lower rates of admission to hospital for myocardial infarction and coronary revascularization in patients with HR ≥ 70 bpm.

Digoxin was found to be independently associated with increased SCD risk. While the specific mechanisms for this association are difficult to identify from the present analysis, it is possible that factors such as older age and severe LVSD contributed to increased vulnerability in the SCD cases. In the DIG (Digitalis Investigation Group) trial, (21,22) where there was no benefit over the long term, the authors postulated that as the trial population aged and creatinine clearance decreased, these factors may have contributed to more pro-arrhythmia. On the other hand, beta₂-agonists are known to increase HR and were previously associated with increased risk of SCD (23,24). Similar to the literature, in the present study, we have found that HR was higher in beta₂-agonists users and that these drugs increased the risk of SCD, but HR remained a significant predictor of SCD, independently of such treatment.

If severe LVSD and rate-affecting drugs do not explain the elevated HR-SCD association, what are the contributing factors? Our findings suggest that there are likely to be additional mechanisms, some yet to be identified, that mediate this association. Higher HR has been associated with development of tachycardia-induced cardiomyopathy, a condition that develops slowly and can be reversible if the HR is controlled. However, recurrent tachycardia can produce a rapid decline in left ventricular function associated with heart failure and sudden death (25). While HR was associated with SCD risk independent of LVSD in the present study, specific mechanisms clearly need further investigation. HR also plays a central role in the cardiovascular system and depends on the balance between vagal and sympathetic tone. Autonomic dysfunction has established involvement in the pathophysiology of SCD (26,27) and impaired HR response during exercise has been associated with overall mortality (28) as well as SCD (29). While autonomic factors are likely to be dynamic, these warrant ongoing investigation. Since resting HR remains a significant predictor, intrinsic or genetic factors may potentially play a confounding role in the association of HR and SCD. The hyperpolarization-activated cyclic nucleotide-gated channel 4 (HCN4) is prominently expressed in the mammalian sino-atrial node and the gene is located on chromosome 15 (30). Mutations in the HCN4 gene are responsible for inherited

sinus bradycardia and five different mutations (573X, D553R, S672R, G480R, A485V) have been recently reported in the literature (31–35). Investigations of genetic factors that may predispose to higher HR also warrant further investigation.

Important strengths of this study include the large sample size, prospective adjudication of SCD cases, and the fact that we used a community-based approach. Moreover, the case-control design allowed the proximity of EKG to the SCD (median within one year) in contrast to published cohort studies (decades prior to event). Given the specific nature of SCD, a case-control design represents an efficient alternative to large cohort studies. In addition, our analysis compared cases of SCD versus controls with CAD, and thus any identified differences are likely to be specific for SCD. However, we acknowledge some limitations. The total duration and dosage of medication could not be systematically assessed.

In conclusion, we have found a significant, strong and graded relationship between increased resting HR and SCD in the general population, even after adjustment for LVSD and rate-modulating drugs. The contributors to elevated HR in patients that suffer SCD warrant further mechanistic evaluation, particularly with a view to discovery of novel heart rate lowering interventions.

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Abbreviations

CAD	Coronary Artery Disease
EF	Ejection Fraction
EMS	Emergency Medical Services
HR	Heart Rate
LVSD	Left Ventricular Systolic Dysfunction
SCD	Sudden Cardiac Death

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Figure 1.
Distribution of HR categories (10 bpm) among SCD cases and controls.
HRs 80–99 bpm or ≥100 bpm were more common in cases ($p<0.0001$).

Figure 2.

Effects of demographic variables and medications on resting HR.

*Significantly greater mean HR among cases compared to controls with an overall mean difference of 7.5 bpm. A difference of at least 7.1 bpm persisted regardless of age, gender, beta-blocker use, and beta2-agonist use (p 0.002).

Table 1

Characteristics of SCD cases vs. controls, Oregon SUDS 2002–2011 (n=756)

Categories	Case	Control	P value*
	n=378	n=378	
Heart Rate (bpm)	76.2±17.4	68.7±16.3	<0.0001
Body Mass Index	29.7±8.0 (n=314)	29.6±6.7 (n=362)	0.80
Smoking			0.11
Current	118 (38.4%)	78 (30.0%)	
Former	120 (39.1%)	114 (43.8%)	
Non-smoker	69 (22.5%)	68 (26.2%)	
Unknown/not evaluated†	71	118	
Diabetes mellitus	168 (44.4%)	120 (31.8%)	0.0003
Abnormal thyroid function	58 (15.3%)	48 (12.7%)	0.29
Hypertension	285 (75.4%)	282 (74.6%)	0.80
COPD/ asthma	154 (40.7%)	100 (26.5%)	<0.0001
Chronic renal insufficiency	102 (27.0%)	62 (16.4%)	0.0004
Liver disease	19 (5.0%)	25 (6.6%)	0.35
Severe LVSD‡	80 (33.2%)	42 (14.6%)	<0.0001
Unknown/not evaluated‡	137	91	
Pharmacological therapies			
Beta-blocker	230 (60.8%)	229 (60.6%)	0.94
Diltiazem	18 (4.8%)	22 (5.8%)	0.52
Verapamil	6 (1.6%)	3 (0.8%)	0.50
Digoxin	62 (16.4%)	12 (3.2%)	<0.0001
Beta2-agonist	76 (20.1%)	55 (14.6%)	0.04

* Results presented as n (%) or mean±SD. Significant differences (p 0.05) among groups based on Pearson chi-square test or Fisher's Exact test for categorical variables and *t*-test for continuous variables.

† For variables with missing values, proportions and p-values are calculated using the non-missing data as the denominator.

‡ Severe LVSD defined as EF < 35%.

Table 2

Multivariable odds ratio estimates for predictors of SCD

Categories	Model I [*] OR (95%CI), P value (n=756)	Model II [†] OR (95%CI), P value (n=528)
HR	1.26 (1.14–1.38), <0.0001	1.18 (1.05–1.33), 0.005
Diabetes	1.35 (0.98–1.87), 0.07	1.53 (1.02–2.28), 0.04
COPD/ asthma	2.04 (1.33–3.12), 0.001	1.89 (1.12–3.17), 0.02
Chronic renal insufficiency	1.57 (1.07–2.31), 0.02	2.26 (1.42–3.60), 0.0005
Digoxin	5.07 (2.64–9.73), <0.0001	4.74 (2.35–9.53), <0.0001
Beta2-agonists	0.77 (0.45–1.31), 0.33	1.23 (0.65–2.33), 0.52
Severe LVSD	---	1.79 (1.11–2.87), 0.02

* Model I include: HR (10 bpm increase), diabetes mellitus, COPD/asthma, chronic renal insufficiency, digoxin, beta2-agonists.

[†] Model II include: Model I variables, severe LVSD.