Novel measure of autonomic remodeling associated with sudden cardiac arrest in diabetes

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BACKGROUND Diabetes is independently associated with an increased risk of sudden cardiac arrest (SCA), with a need to identify novel methods for risk stratification. Diabetic patients can develop autonomic dysfunction that has been associated with an increased risk of ventricular arrhythmogenesis and manifests as reduced heart rate variability (HRV). However, previously published studies have not accounted for resting heart rate (HR), important from both pathophysiological and prognosticating standpoints.

OBJECTIVE We sought to evaluate autonomic remodeling of the sinus node response in SCA and diabetes while accounting for HR.

METHODS We performed a case-control study in SCA cases (age 35–59 years; 2002–2014) from the ongoing Oregon Sudden Unexpected Death Study (catchment population ~1 million), and archived 12-lead electrocardiograms recorded prior to the SCA event were compared with those of geographic controls. Short-term HRV was calculated from digitized 10-second electrocardiograms by using established methods. We analyzed 313 subjects (mean age 52.0 ± 5.5 years; 216 men, 69.0%) and compared 4 groups: 111 diabetic (49 cases, 62 controls) and 202 nondiabetic (80 cases, 122 controls) subjects.

RESULTS Analysis of covariance showed an absence of the expected interaction between HRV and HR (HRV-HR) in diabetic patients with SCA (regression slope −0.008; 95% confidence interval −0.023 to 0.0071; $P = .26$). This finding, unique to this population of diabetic patients with SCA, was not detected using traditional HRV measures.

CONCLUSION By incorporating resting HR in this analysis, we observed that this population of diabetic patients with SCA had loss of the expected HRV-HR relationship. This potentially novel noninvasive risk measurement warrants further investigation, especially at the level of the individual patient.

KEYWORDS Sudden cardiac arrest; Heart rate variability; Diabetes; Electrocardiogram; Sudden death; Risk stratification

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Introduction

Sudden cardiac arrest (SCA) remains a major cause of mortality, resulting in an estimated 300,000 to 350,000 deaths each year in the United States.[1] Hence, risk identification and prevention are the cornerstones of SCA management, especially in middle-aged subjects who are most likely to suffer these lethal events as their first and final manifestation of heart disease.[2] Diabetes is a major independent risk factor for SCA.[3–5] One of the complications of diabetes is cardiac autonomic neuropathy (CAN),[6] which is a potential mediator of the increased risk of SCA associated with diabetes.[7] Therefore, the potential role of CAN-related abnormalities in risk stratification of SCA needs focused evaluation.

Several heart rate variability (HRV) measures have been used to assess cardiac autonomic dysfunction and to diagnose CAN.[7] However, in normal populations HRV increases as baseline heart rate (HR) decreases. This association between baseline HR and HRV, which for convenience we can term HRV-HR, has been largely ignored in previous analyses.[8,9] Moreover, it is well established that increased resting HR is associated with increased all-cause mortality and SCA,[3,10,11] making it difficult to evaluate the effect of HRV on SCA without examining the relationship between HRV and HR.[9,12]

Reduced HRV is a predictor of ventricular arrhythmias and SCA, but also nonarrhythmic mortality in various subgroups of patients[5,13–16]; and it is not presently recommended as a tool for risk stratification of SCA.[17] Traditionally, HRV is quantified using spectral analysis from long-term electrocardiographic

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(ECG) monitor data providing measures of both sympathetic and parasympathetic contributions to HRV.[18] However, it is difficult to obtain such measurements in feasible numbers of patients who suffer SCA, an unexpected condition that often occurs without warning. Consequently, HRV from the standard 10-second ECG was suggested to be a practical substitute for the assessment of cardiac vagal tone, which is the major contributor to the high-frequency component of HRV.[19]

To analyze the risk of SCA associated with this new marker, we compared HRV-HR obtained from a standard 12-lead ECG in diabetic cases with SCA, nondiabetic cases with SCA, as well as diabetic and nondiabetic control subjects.

Methods

Study population

The Oregon Sudden Unexpected Death Study is an ongoing, prospective, population-based study of SCA in the Portland, OR, metropolitan region (regional population ~1 million). Detailed descriptions of subject recruitment and methodologies have been described in previous publications.[20,21] In brief, patients with out-of-hospital cardiac arrests in the Portland, OR, metropolitan region were identified through the emergency medical services system, the state medical examiner's office, and 16 hospital emergency departments in the region. All potential SCA cases were then adjudicated by 3 physicians on the basis of complete medical records including prehospital and in-hospital records. SCA was defined as a sudden unexpected pulseless state due to likely cardiac causes. Patients with unwitnessed arrests must have been seen in their usual state of health within 24 hours of the event, and individuals with likely noncardiac causes of death such as trauma, chronic terminal illness, or drug overdose were excluded. Concurrently, control subjects were selected from the same geographic location. A majority of control subjects had prevalent coronary artery disease (CAD), since prior studies have shown that CAD is responsible for a large majority of SCA in both diabetic and nondiabetic patients.[22] Control subjects with documented CAD were selected from all potential eligible patients who visited cardiology outpatient clinics or who had coronary angiography at a regional health care system or (from 2003 to 2006) were transported by emergency medical services because of complaints of angina. All eligible CAD controls who consented were enrolled, regardless of age or sex. In addition, control subjects with and without prevalent CAD were enrolled (from 2009 to present) from a randomly selected list of members in a large health maintenance organization, frequency-matched by age and sex to the case population. CAD was defined by ≥50% stenosis in a large coronary vessel or prior coronary artery bypass graft, myocardial infarction, or percutaneous coronary intervention. All available medical records were reviewed in detail for the presence of diabetes or diabetic medications and each patient adjudicated for presence of diabetes, defined as specific documentation of diabetes in the medical record or the use of insulin or other hypoglycemic agents. Patients with prior ventricular arrhythmias or SCA were excluded from the control population.

Subjects included in the present analysis were aged 35–59 years with a sinus rhythm ECG available prior to arrest, and all clinical information was gathered from a comprehensive and systematic review of medical records. For patients with multiple prior ECGs, the one closest to and prior to cardiac arrest for cases and closest to day of ascertainment for controls was used. Diabetes was adjudicated if there was a documentation of diabetes in the medical records or the use of insulin or other hypoglycemic agents. Obesity was defined as body mass index ≥30 kg/m^2. The institutional review boards of Cedars-Sinai Medical Center, Oregon Health and Science University, and all other relevant health systems approved the study.

ECG analysis

Twelve-lead ECG tracings at 25 mm/s paper speed and 10 mm/mV amplitude recorded during routine clinical practice closest to or prior to SCA were scanned with a minimum resolution of 300 dots/in and were digitized using ECGScan (Amps LLC). For controls, ECGs were recorded at the time of enrollment in the study or were obtained from the most recent clinical visit. The QT interval was measured manually and corrected for HR using the Bazett formula.[23] Digitized tracings were reviewed by a trained, blinded physician to ensure accuracy and then imported into MATLAB version R2013a (MathWorks Inc, Los Angeles, CA) for further analysis. R waves were automatically detected using an open-source, wavelet-based detection algorithm and then manually verified by another trained, blinded physician.[24,25] R-R intervals were calculated on the basis of the continuous lead with the largest amplitude R-wave deflection. Baseline HR was calculated from the average of all detected R-R intervals. ECGs were required to have at least 6.67 seconds of consecutive sinus rhythm without premature ventricular or premature atrial contractions to be included in the final analysis. A cutoff time of 6.67 seconds was chosen to include all signals from the high-frequency domain in HRV spectral analysis, which spans from 0.4 to 0.15 Hz (6.67 seconds = 1/0.15 Hz). ECGs were excluded if they did not have a continuous rhythm strip owing to concerns for inconsistent R-R interval measures between leads.

Definitions of standard time-domain measures of HRV

Standard deviation of all R-R intervals (SDNN): Computed standard deviation of all R-R intervals in the recording.[26]

Root mean square differences of successive R-R intervals (rMSSD): The square root of the mean of sum of the squares of differences between adjacent R-R intervals in the recording.[26]

Maximal difference: Absolute difference between the longest and the shortest R-R interval measured in the duration.[26]

Normalizing HRV for baseline HR

As baseline HR has been shown to account for up to 30% of HRV, we applied previously published heart rate–normalizing

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