Electrocardiographic QT Interval Prolongation and Risk of Primary Cardiac Arrest in Diabetic Patients

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Sudden cardiac death, also known as primary cardiac arrest (PCA), is a major cause of mortality among diabetic patients and typically occurs in the setting of coronary heart disease. Because it can occur as the first clinical manifestation of coronary heart disease, identifying diabetic patients at risk of PCA remains challenging. Interrelated sequelae of diabetes, including QT prolongation and autonomic failure (1,2), have been repeatedly implicated in the pathophysiology of PCA (3–6). However, it remains unknown whether the QT interval on a 12-lead electrocardiogram (ECG) has potential utility in risk stratification of diabetic patients without prior physician-diagnosed heart disease for PCA (7–12).

RESEARCH DESIGN AND METHODS

— We therefore conducted a case-control study of PCA in a large prepaid health plan, Group Health Cooperative of Puget Sound. We included patients age 18–79 years who were enrolled for ≥1 year or had four or more clinic visits in the prior year, had physician-diagnosed diabetes noted in their ambulatory care medical record or were treated with oral hypoglycemics or insulin, and had an ECG recorded before their index date (see below). We excluded enrollees with prior physician-diagnosed heart disease (Table 1).

Patients were diabetic enrollees who experienced out-of-hospital PCA (a sudden, pulseless condition without a known noncardiac cause) between 1 January 1980 and 31 December 1994. We identified potential cases from Seattle and suburban King County emergency medical service incident reports and Group Health Cooperative of Puget Sound death records. Potential control subjects were a stratified random sample of diabetic enrollees, frequency matched to all cases within groups defined by age in decades, sex, and index year. We used information from ambulatory care medical records, physician-reviewed emergency medical service incident reports, and autopsy reports (when available) to exclude patients with prior, noncardiac, life-threatening conditions (13). We defined an index date for each case as the date of PCA. We randomly assigned an index date to each control subject from the distribution of case index dates.

Abstractors recorded clinical characteristics and laboratory values of enrollees before the index date from ambulatory care medical records. The EPICARE Center estimated the QT index (QTI; %) and the T-wave negativity, ST-segment depression, and Q-wave scores (unitless) from photocopied ECGs according to Novacode criteria (14,15). We determined treatment with medications at the index date using computerized pharmacy records. These measures have been defined and their characteristics described elsewhere (16–21).

RESULTS

— Cases (n = 79) and control subjects (n = 214) were similar in age (65.4 ± 0.6 vs. 65.7 ± 0.3 years), race (90 vs. 94% white), smoking status (22 vs. 17% current), history of type 2 diabetes (97 vs. 98%), hypertension (52 vs. 52%), systolic/diastolic blood pressure (142 ± 2 vs. 143 ± 1/80 ± 1 vs. 81 ± 1 mmHg), and BMI (27.6 ± 0.6 vs. 28.8 ± 0.4 kg/m^2). However, cases had longer duration diabetes (11.6 ± 1.2 vs. 9.0 ± 0.7 years, P = 0.07), more metabolic complications (14 vs. 6%, P = 0.03), and cerebrovascular disease (33 vs. 7%, P < 0.01). Although the ECG date–index date interval was similar in cases and control subjects (5.1 ± 0.6 vs. 5.5 ± 0.5 years), cases also had a higher mean heart rate (80 ± 2 vs. 75 ± 1 bpm, P = 0.02), QTI (109 ± 1 vs. 103 ± 1%, P < 0.01), Q-wave score (6.5 ± 0.9 vs. 3.7 ± 0.6, P = 0.01), ST-segment depression score (4.0 ± 0.7 vs. 1.9 ± 0.4, P = 0.01), and T-wave negativity score (4.0 ± 0.8 vs. 2.1 ± 0.5, P = 0.04). Remaining ECG, medication, lab, and clinical measures were comparable.

In conditional logistic regression models adjusted for sampling design, age, and race, risk of PCA was increased 3.5 (1.6–7.6)-fold in the fourth versus first QTI quartile, but there was little evidence of increased risk for diabetic patients in the second and third quartiles (Table 1).

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Abbreviations: ECG, electrocardiogram; PCA, primary cardiac arrest; QTI, QT index.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Risk of PCA in diabetic enrollees* by QTI quartile†*

QTI (%)	QT_c (ms)	*n* (%)		Adjustment (OR [95% CI])			
		Cases	Control subjects	Age and race	Clinical	ECG	Autonomic
≤99	391 ± 2	12 (15)	54 (25)	1.0	1.0	1.0	1.0
99–103	418 ± 1	10 (13)	53 (25)	0.8 (0.3–2.1)	0.9 (0.3–2.7)	1.0 (0.3–2.9)	0.9 (0.3–2.7)
103–107	436 ± 1	14 (18)	47 (22)	1.1 (0.5–2.7)	1.3 (0.5–3.6)	1.2 (0.4–3.3)	1.2 (0.4–3.4)
>107	476 ± 3	43 (54)	60 (28)	3.5 (1.6–7.6)	3.3 (1.3–8.5)	2.8 (1.0–7.9)	2.8 (1.0–7.6)

Data are %, means ± SD, or OR (95% CI). *Excludes enrollees with physician-diagnosed heart disease (angina, myocardial infarction, cardiomyopathy, congestive heart failure, arrhythmia, coronary angioplasty, coronary artery bypass graft, or treatment with digoxin or nitrates before their index date). †Defined by the 25th-75th percentiles in control subjects. All models adjusted for sampling design. Specific models also adjusted for age (years), race (age and race), and in addition, current smoking, hypertension, diastolic blood pressure (mmHg), BMI (kg/m^2), diabetes type, diabetes duration (years), retinopathy, metabolic complications (hospitalization for hypoglycemia, hyperglycemia, hyperosmolar coma, or ketoacidosis), cerebrovascular disease, peripheral vascular disease, glucose (mg/dl), creatinine (mg/dl), dipstick protein ≥ trace, and prescriptions for oral hypoglycemics, insulin, and ACE inhibitors (clinical). The model adjusting for ECG characteristics (ECG) also included the T-wave negativity score, ST-segment depression score, and Q-wave score, whereas the model adjusting for autonomic characteristics (autonomic) also included history of symptomatic dysautonomia (orthostatic hypotension, syncope, gastroparesis, diabetic diarrhea, or atonic bladder), prescriptions for β-blockers and tricyclic antidepressants, heart rate (bpm), and RR variation (ms). All continuous variables were centered on their means. $QTI = (QT \div QT_{predicted}) \times 100$, where $QT_{predicted} = 656 \div (1 + 0.01 \times \text{heart rate})$.

Effects of further adjustment were modest (Table 1). Comparing the upper with the lower three quartiles combined produced similar findings but narrowed the 95% confidence limits around the point estimates: 3.6 (2.0–6.3) (age and race), 3.1 (1.6–6.1) (clinical), 2.7 (1.2–5.9) (ECG), and 2.7 (1.3–5.4) (autonomic). Effects of controlling for the ECG date–index date interval, substituting Bazett's heart-rate corrected QT (QT_c) for QTI (22,23) and weighting for the probability of ECG availability (24,25) were negligible.

CONCLUSIONS — This is the first population-based study to examine the risk of PCA associated with QT prolongation in predominantly type 2 diabetic patients without prior physician-diagnosed heart disease (26). Diabetic patients in the upper quartile of the QTI distribution (i.e., with a QTI >107%) had a threefold increased risk of PCA after accounting for clinical and other ECG or autonomic characteristics.

Whether the increased risk reflects direct effects of previously undiagnosed myocardial damage, autonomic failure, or both remains unknown, but we excluded enrollees with prior physician-diagnosed heart disease and were unable to attribute the association to differences in clinical characteristics or subclinical ischemia and infarction. Similarly, adjustment for symptomatic dysautonomia, use of β-blockers and tricyclic antidepressants, and measures of heart rate and RR variation only modestly attenuated the increased risk of PCA. Moreover, results were unchanged by controlling for the ECG date–index date interval, substituting QT_c, or weighting for ECG availability.

These findings suggest that QT prolongation may be useful in risk stratifying populations of predominantly white, type 2 diabetic patients for PCA. Whether the findings are generalizable to diabetic patients who are nonwhite and those with prior angina, myocardial infarction, and/or congestive heart failure remains unknown. Further research is needed to determine whether clinical interventions to reduce QTI (2,27–29) decrease the risk of PCA among diabetic patients.

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