Relation Between QT Interval Variability and Cardiac Sympathetic Innervation in Patients with Diabetes Mellitus

Mathias Baumert[1], Julian Sacre[2], Bennett Franjic[2]

[1]The University of Adelaide, Adelaide, Australia
[2]University of Queensland, Brisbane, Australia

Abstract

Elevated QT interval variability (QTV) has been associated with increased cardiac mortality, but the underlying mechanisms are incompletely understood. Sympathetic activity is thought to be a main contributor to QTV. The aim of this study was to investigate the relation between cardiac sympathetic integrity and QTV in 15 patients with type 2 diabetes mellitus and varying degrees of cardiac autonomic neuropathy. Cardiac sympathetic innervation was assessed by ^{123}I-mIBG scintigraphy based on heart-to-mediastinum ratio of ^{123}I-mIBG uptake 4 hours after infusion. To assess QTV high resolution ECGs (1000 Hz) were recorded during standing. Beat-to-beat QT intervals were calculated over a period of 5 minutes, using a template-stretching algorithm. QTV was quantified using time and frequency domain measures as well as non-linear approaches (symbolic dynamics, fractal dimension). The group mean and standard deviation of HMR values were 1.07 ± 0.48*. Time and frequency domain QTV parameters were significantly increased in subjects with sympathetic dysinnervation and inversely correlated with HMR (*$r = -0.7, p < 0.001$*). In conclusion, there is a clear link between sympathetic dysinnervation and elevated QTV in patients with type 2 diabetes mellitus during sympathetic activation. Sympathetic dysinnervation is associated with increased ventricular repolarization lability.*

1. Introduction

QT interval variability reflects temporal fluctuations in the duration of ventricular repolarization. Elevated QT variability has been associated with increased sudden cardiac death risk in chronic heart failure [1] and ventricular arrhythmogenesis in patients with structural heart disease [2]. The origins of QT variability, particularly the influences of autonomic nervous system activity, remain incompletely understood. Acute elevation of QT variability has been observed in response to sympathetic activation [3] and in disease states characterized by sympathetic overactivity [1, 2]. Conflicting results on associations with cardiac norepinephrine spillover, the gold standard in assessment of cardiac sympathetic activity, have been reported. Positive correlations were described in hypertension [4] but not major depression/panic disorder [5]. The cardiac autonomic neuropathy (CAN) of type 2 diabetes mellitus (T2DM) is independently associated with poor prognosis [6]. Vagal impairment of cardiac control can be readily assessed by measuring heart rate variability [7]. Sympathetic involvement in CAN may be identified with high specificity by radionuclide imaging using the tracer iodine 123-metaiodobenzylguanidine (^{123}I-mIBG), which shares the neuronal uptake and storage mechanisms of norepinephrine. Reduced heart rate variability as well as globally reduced cardiac uptake of ^{123}I-mIBG, consistent with vagal and sympathetic dysinnervation, have been identified in patients with diabetes mellitus [6]. In a recent study we reported negative correlations between cardiac ^{123}I-mIBG uptake and QT variability in patients with T2DM, suggestive of an association between myocardial sympathetic dysinnervation and repolarization lability. [8]. Importantly, this association was only observed during a period of sympathetic activation (i.e. standing), but not during rest. The aim of this study was to further identify specific features of QT interval variability that might be primarily reflective of sympathetic dysinnervation.

2. Methods

2.1. Subjects

Subjects with T2DM ($n = 15$) with no history of cardiovascular disease, cancer or psychiatric or other severe illness were recruited from the community (Table 1). ^{123}I-mIBG imaging and heart rate variability data for this cohort has been reported previously [9]. Exercise echocardiography studies were performed in all patients to verify normal ejection fraction ($> 50\%$) and the absence of coronary artery disease (i.e. no inducible wall motion abnormalities indicative of ischemia). Patients provided written informed consent and the study protocol was approved by

Table 1. Patient characteristics.

Male [%]	60
Age [yrs]	57.9 ± 8.1
Diabetes duration [yrs]	7 [6-14]
HbA1c [mmol/mol]	8.2 ± 2.2
BMI [kg/m^2]	30.2 ± 5.4
Heart rate [bpm]	71 ± 12
Systolic BP [mmHg]	125 ± 19
Diastolic BP [mmHg]	72 ± 9
Hypertension [%]	9
Heart-to-mediastinum ratio	1.84 ± 0.16

Table 2. QT variability measures.

meanQT	mean QT interval duration, in s
sdQT	standard deviation of QT intervals, in s
RMSSD	RMS of QT interval differences, in s
LF	low frequency power, in s^2
HF	high frequency power, in s^2
D_H	Higuchi's fractal dimension
0V	words with zero variation, in %
1V	words with one variation, in %
2LV	words with 2 likewise variations, in %
2ULV	words with 2 unlike variation, in %

hospital and university human research ethics committees.

2.2. ^{123}I-MIBG imaging

Protocols for recording and analysis of ^{123}I-mIBG images have been described in detail [9]. Patients were premedicated with 600 mg potassium perchlorate to block thyroid uptake of radioiodine. A low-energy, high-resolution collimator (Symbia, Siemens, Erlangen, Germany) was used in the acquisition of anterior planar and single photon emission computed tomography (SPECT; 32 projections for 50 s each) images 15 minutes (early) and 4 hours (delayed) following injection of 150 MBq of ^{123}I-mIBG. Global cardiac uptake of ^{123}I-mIBG was calculated from both early and delayed planar images by the ratio of tracer activity (mean count per pixel) in the heart and mediastinum. Due to non-neuronal uptake affecting early images, the delayed heart-to-mediastinum ratio (HMR) was primarily used in analyses and to define the presence of cardiac sympathetic dysinnervation (HMR < 1.8) [10].

2.3. ECG recording and QT variability analysis

Studies were performed in accordance with standard conditions for clinical autonomic testing. Subjects were assessed in the morning and following a light meal and administration of diabetes medications. Pre-test abstinence from smoking and caffeine (12 hours), and alcohol, heavy exercise and anti-hypertensive medications (24 hours) was required. Following at least 20 minutes supine rest in a quiet room, an ECG (lead II) was recorded continuously over 5-minutes during standing at a sampling frequency of 1kHz using a Powerlab 8SP data acquisition system linked with commercially available software (LabChart Pro v6.1.3, AD Instruments, Sydney, Australia). After visual inspection of all ECG recordings to remove artifacts, beat-to-beat QT intervals were calculated using the algorithm proposed by Berger et al [1]. Here, an operator-defined QT interval template is selected for one beat based on the beginning of the QRS complex and the beginning and end of the T wave. The algorithm then calculates the QT intervals of all other beats by determining the degree to which the template must be stretched or compressed in time to optimally match each T wave. In contrast with alternative methods, consideration of the whole T wave enables a relatively robust estimation of beat-to-beat QT interval changes. Of the beat-to-beat QT interval time series we computed the measures summarized in Table 2.3.

Time and frequency domain measures were computed according to the Heart Rate Variability Task Force guidelines [11]. To compute the fractal dimension D_H of a graph, Higuchi considers a finite set of observations $X(j), j = 1, 2, ..., N$ taken at a regular interval k, and evaluates the length $L_m(k)$ of the corresponding graph for different interval lengths k from sequences X_m^k : $X(m), X(m+k), X(m+2k), ..., X(m+\left[\frac{N-m}{k}\right])$, where $m = 1, 2, ..., k$ and $\left[\frac{N-m}{k}\right]$ denotes the integer part of $(N-m)/k$. The length of the graph is calculated as

$$L_m(k) = \left(\sum_{i=1}^{\left[\frac{N-m}{k}\right]} |X(m+ik) - X(m+(i-1)k)| \right) \frac{N-1}{\left[\frac{N-m}{k}\right] k^2}. \quad (1)$$

If the behaviour of the graph has fractal characteristics over the available range k then

$$L(k) \propto k^{-D_H}, \quad (2)$$

where D_H is the fractal dimension and $L(k)$ is the average value over k partial lengths of the graph. For a straight line, $D_H = 1$. For Brownian motion, $D_H = 1.5$, and for Gaussian white noise, D_H saturates at two. For time series with $1/f^\beta$ power spectra, $D_H = (5-\beta)/2$. This relationship is valid for $1 < \beta < 3$. Numerical experiments have shown that time series with the same β can show different D_H values depending on the phase distribution [12]. We have previously employed Higuch's fractal dimension to measure the roughness of R-R time series

[13]. For symbolic analysis of QTV we employed the approach proposed by Porta *et al.* [14]. Time series of QT intervals were transformed into an alphabet of 6 symbols 0, 1, 2, 3, 4, 5. As a transform rule nonuniform quantization was applied, keeping constant the number of points associated with each quantization level. All the patterns (symbolic sequences) with a length of three were grouped into four families according to the number and types of variations from one symbol to the next. The pattern families are: 1) patterns with no variation (0V—all three symbols are equal); 2) patterns with one variation (1V—two consecutive symbols are equal and the remaining one is different); 3) patterns with two like variations (2LV—the three symbols form an ascending or descending ramp), 4) patterns with two unlike variations (2ULV—the three symbols form a peak or a valley).

2.4. Statistics

For statistical analysis we computed mean values and standard deviations of QTV measures as well as ^{123}I-mIBG markers. To investigate the relationship between QTV measures and cardiac sympathetic dysinnervation, we computed Pearson's correlation coefficients.

3. Results

Patients displayed a wide range of cardiac ^{123}I-mIBG uptake, ranking from normal (HMR > 1.8; $n = 9$) to abnormal (HMR < 1.8; $n = 5$). Measures of QTV are displayed in Table 3 subdivided based on presence of sympathetic dysinnervation (Table3) All time and frequency domain measures indicate elevated QTV in patients with sympathetic dysinnervation. Non-linear measures, which assess the complexity rather than the magnitude of QTV show no significant group differences Pearson's correlation coefficients as indicated in the last column of Table 3 show a similar degree of correlation between all QTV time and frequency domain measures and HMR around $r = 0.7$, with the exception of HF. None of the complexity measures shows a significant correlation with HMR.

Table 3. Group means and standard deviations of QT variability measures in patients with normal sympathetic innervation (T2DM+) and with sympathetic dysinnervation (T2DM-), t-test p-values as well as Pearson's correlation coefficient r with HMR.

	T2DM+	T2DM-	p	r
meanQT	356.2 ± 33.2	378.0 ± 33.2	0.16	-0.38
sdQT	3.6 ± 0.8	6.7 ± 0.8	0.02	-0.75
RMSSD	2.9 ± 1.4	7.7 ± 1.4	0.01	-0.77
LF	0.9 ± 0.4	4.6 ± 0.4	0.01	-0.71
HF	1.4 ± 1.1	5.4 ± 1.1	0.07	-0.57
D_H	1.9 ± 0.1	2.0 ± 0.1	0.09	-0.33
0V	32.9 ± 14.6	25.1 ± 14.6	0.30	0.23
1V	39.5 ± 4.7	42.0 ± 4.7	0.32	-0.19
2LV	4.3 ± 3.5	6.2 ± 3.5	0.45	-0.26
2ULV	23.3 ± 9.2	26.7 ± 9.2	0.43	-0.13

4. Discussion and conclusions

The main finding of our study is that magnitude rather than complexity of beat-to-beat QT interval variability elicited by sympathetic activation is associated with sympathetic dysinnervation. Time and frequency domain analysis of QTV suggest a lack of a specific frequency range being primarily responsible for this association. Assessment of QTV complexity and its lack of association with ^{123}I-mIBG uptake further suggests that there is no specific temporal pattern of QTV indicative of sympathetic dysinnervation. In a recent study we investigated temporal dynamics of QTV by means of detrended fluctuation analysis and multiscale entropy and observed no long-range correlations and multiscale entropy patterns, which were similar to those of random data [15]. Despite the close physiological relationship between average heart rate and average QT interval, temporal short-term dynamics differ notably, the latter being more erratic. With regard to sympathetic involvement in the generation of QTV, our current findings point towards a rather non-specific association.

Our data support the hypothesis that QT variability reflects sympathetic function in the context of acute or chronic sympathetic activation, as with standing, selective pharmacological intervention, or disease. However, ^{123}I-mIBG scintigraphy is not synonymous with measuring sympathetic activity per se, but instead reflects the holistic integrity of postganglionic presynaptic sympathetic nerve terminals, including norepinephrine uptake, storage and release mechanisms [16]. Indeed, the dysinnervation identified by low HMR in our patients may relate to structural, rather than functional defects, characterized by anatomical neuronal loss (i.e. denervation).

In conclusion, there is a clear link between sympathetic dysinnervation and elevated QTV in patients with type 2 diabetes mellitus during sympathetic activation. Sympathetic dysinnervation is associated with increased ventricular repolarization lability.

Acknowledgements

This study was partly supported by a grant from the Australian Research Council (110102049).

References

[1] Berger RD, Kasper EK, Baughman KL, Marban E, Calkins H, Tomaselli GF. Beat-to-beat QT interval variability: novel evidence for repolarization lability in ischemic and nonischemic dilated cardiomyopathy. Circulation 1997;96:1557–65.

[2] Tereshchenko LG, Fetics BJ, Berger RD. Intracardiac QT variability in patients with structural heart disease on class III antiarrhythmic drugs. J Electrocardiol 2009;42:505–510.

[3] Yeragani VK, Pohl R, Jampala VC, Balon R, Kay J, Igel G. Effect of posture and isoproterenol on beat-to-beat heart rate and QT variability. Neuropsychobiology 2000;41:113–123.

[4] Baumert M, Schlaich MP, Nalivaiko E, Lambert E, Sari CI, Kaye DM, Elser MD, Sanders P, Lambert G. Relation between QT interval variability and cardiac sympathetic activity in hypertension. Am J Physiol Heart Circ Physiol 2011:300:H1412–1417.

[5] Baumert M, Lambert GW, Dawood T, Lambert EA, Esler MD, McGrane M, Barton D, Nalivaiko E. QT interval variability and cardiac norepinephrine spillover in patients with depression and panic disorder. Am J Physiol Heart Circ Physiol 2008;295:H962–H968.

[6] Mantysaari M, Kuikka J, Mustonen J, Tahvanainen K, Vanninen E, Lansimies E, Uusitupa M. Noninvasive detection of cardiac sympathetic nervous dysfunction in diabetic patients using [123I]metaiodobenzylguanidine. Diabetes 1992;41:1069–1075.

[7] Javorka M, Trunkvalterova Z, Tonhajzerova I, Javorkova J, Javorka K, Baumert M. Short-term heart rate complexity is reduced in patients with type 1 diabetes mellitus. Clin Neurophysiol. 2008;119:1071–81.

[8] Sacre JW, Franjic B, Coombes JS, Marwick TH, Baumert M. QT interval variability index is associated with 123I-MIBG cardiac sympathetic activity in type 2 diabetes. European Society of Cardiology Meeting, Paris 2011.

[9] Sacre JW, Franjic B, Jellis CL, Jenkins C, Coombes JS, Marwick TH. Association of cardiac autonomic neuropathy with subclinical myocardial dysfunction in type 2 diabetes. JACC Cardiovasc Imaging 2010;3:1207–1215.

[10] Scholte AJ, Schuijf JD, Delgado V, Kok JA, Bus MT, Maan AC, Stokkel MP, Kharagitsingh AV, Dibbets-Schneider P, van der Wall EE, Bax JJ. Cardiac autonomic neuropathy in patients with diabetes and no symptoms of coronary artery disease: comparison of 123I-metaiodobenzylguanidine myocardial scintigraphy and heart rate variability. Eur J Nucl Med Mol Imaging 2010;37:1698–1705.

[11] Malik M. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J 1996;17:354–81.

[12] Higuchi T. Relationship between the fractal dimension and the power law index for a time series: a numerical investigation. Physica D 1990;46,254–264.

[13] Baumert M, Wessel N, Schirdewan A, Voss A, Abbott D. Scaling characteristics of heart rate time series before the onset of ventricular tachycardia. Ann Biomed Eng 2007;35:201–207.

[14] Porta A, Tobaldini E, Guzzetti S, Furlan R, Montano N, Gnecchi-Ruscone T. Assessment of cardiac autonomic modulation during graded head-up tilt by symbolic analysis of heart rate variability. Am J Physiol Heart Circ Physiol. 2007;293:H702–H208.

[15] Baumert M, Javorka M, Seeck A, Faber R, Sanders P, Voss A. Multiscale entropy and detrended fluctuation analysis of QT interval and heart rate variability during normal pregnancy. Comput Biol Med. 2011 Apr 28

[16] Wakabayashi T, Nakata T, Hashimoto A, Yuda S, Tsuchihashi K, Travin MI, Shimamoto K. Assessment of underlying etiology and cardiac sympathetic innervation to identify patients at high risk of cardiac death. J Nucl Med 2001;42:1757–1767.

Address for correspondence:

Mathias Baumert

The University of Adelaide

School of Electrical and Electronic Engineering

SA 5005, Australia

E-mail address: mbaumert@eleceng.adelaide.edu.au