Abnormal autonomic modulation of QT interval in patients with idiopathic ventricular tachycardia associated with clinically normal hearts

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Abstract

Background—Idiopathic ventricular tachycardia (VT) occurs in a small but important subset of patients without clinically overt heart disease. The mechanism of the arrhythmogenesis remains unclear in these patients. This study examines modulation of the QT interval by the autonomic nervous system in a group of patients with idiopathic ventricular tachycardia.

Methods—Cardiac autonomic activity and ventricular repolarisation were studied in 27 patients with VT associated with a clinically normal heart (NHVT) and in 20 normal subjects. All the patients were in sinus rhythm, had normal atrioventricular conduction, and were in a drug free state. Cardiac efferent autonomic activity was measured by spectral analysis of heart rate variability from 24 hour ambulatory electrocardiograms on a Holter analysis system (Marquette). Ventricular repolarisation was evaluated by measuring the QT intervals from the same 24 hour Holter tapes at one hour intervals.

Results—There was no difference in any of the QT interval variables including the maximum, minimum, and mean of both the QT interval and its corrected value (Bazett's formula) between patients with NHVT and normal subjects. The high frequency component (0.04–0.15 Hz) of heart rate variability was significantly decreased in patients with NHVT compared with normal subjects (16 (8) v 21 (12) ms, $p < 0.05$). There was a significant correlation between the spectral variables of heart rate variability and the mean, maximal, and minimal QT intervals in normal subjects, whereas the relation was lost in patients with NHVT. No difference was found in mean heart rate between normal subjects and patients with NHVT (70 (9) v 72 (13) beats/min, NS).

Conclusions—The high frequency component of heart rate variability is significantly decreased and the relation of QT interval to heart rate variability is significantly altered in patients with NHVT as compared with normal subjects. These findings suggest that abnormal modulation of the QT interval by the autonomic nervous system may play an important part in the arrhythmogenesis of NHVT. This might result from

impaired vagal efferent cardiac activity in these patients.

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Idiopathic ventricular tachycardia (VT) occurs in a small but important subset of patients with a clinically normal heart (NHVT).^{1,2} Conditions considered possible as a cause of this arrhythmia include undiagnosed coronary artery disease, unrecognised cardiomyopathy, subclinical myocarditis, localised myocardial disease, and mild mitral valve prolapse.¹ The significance of these abnormalities in the genesis of the arrhythmia is uncertain,¹ and the mechanism of arrhythmogenesis in NHVT remains unclear.^{1,2}

Normal and abnormal heart rhythms are subject to the influences of the autonomic nervous system.³ Alteration of ventricular repolarisation also plays an important part in both arrhythmogenic and antiarrhythmic mechanisms. There is evidence for an imbalance of cardiac autonomic activity in patients with NHVT.⁴ Perhaps abnormal autonomic activity results in inappropriate modulation of ventricular repolarisation and thus a predisposition to arrhythmia in these patients. To examine this hypothesis, autonomic activity and ventricular repolarisation were studied in 27 patients with NHVT and in 20 normal subjects. Cardiac efferent autonomic activity was measured by spectral analysis of heart rate variability from 24 hour Holter tapes, and ventricular repolarisation was evaluated by measuring QT intervals from the same 24 hour Holter tapes at one hour intervals.

Patients and methods

PATIENTS

Group I (control group) consisted of 20 clinically normal subjects (10 men and 10 women), mean (SD) age 39 (13) (range 16–68) years. None had appreciable cardiac or other medical problems and their 24 hour ambulatory electrocardiograms were all normal and without evidence of arrhythmia.

Group II consisted of 27 patients (15 men and 12 women) with NHVT, aged 39 (14) (range 16–72) years. There were no significant differences in age and sex between groups I and II. None of these patients had a history of heart disease.

All patients had a normal clinical examination, normal chest radiography, and normal resting electrocardiograms. Patients with

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autonomic neuropathy, atrial fibrillation, sinus node dysfunction, a cardiac pacemaker, or intraventricular conduction delay were excluded. No patient had angiographic evidence of coronary artery disease, reduced left ventricular ejection fraction, or regional wall motion abnormality during left ventricular cineangiography as assessed by two independent observers. The VT was non-sustained in 12 patients (group II_a) and sustained in the other 15 (group II_b). Non-sustained VT was defined as broad QRS complexes that occur at a rate of more than 120 beats/min, last more than three beats but less than 30 s, and end spontaneously without haemodynamic compromise. Sustained VT was defined as QRS complexes that occur at a rate of more than 120 beats/min, last more than 30 s, or require intervention to end them because of haemodynamic instability.

Cardiac biopsy specimens showed normal histology in all but four patients in whom mild non-specific fibrosis was found.

ANALYSIS OF HEART RATE VARIABILITY

All subjects underwent two channel (modified V₅ and V₁ leads) 24 hour ambulatory electrocardiographic monitoring in a drug free state. All patients were in sinus rhythm and had normal atrioventricular conduction. Heart rate variability was analysed from the 24 hour ambulatory electrocardiogram with a Holter analysis system (Marquette Series 8000). After classification of the QRS morphology, the longest and the shortest RR intervals on the RR interval histogram were manually confirmed until no QRS complex was mislabelled as either an artifact or a supraventricular ectopic beat. The largest and the smallest RR ratios on the RR ratio histogram were also visually checked to ensure all normal and abnormal QRS complexes on the ambulatory electrocardiograms were correctly labelled. When calculating the heart rate variability measurements, we used only normal to normal intervals. Each interval that was to be excluded due to ectopic beats or artifacts was replaced by holding the previous coupling interval level throughout the time interval to the next valid coupling interval. The beat to beat fluctuations were converted to frequency domain by the fast Fourier transformation and the spectral measures were computed as the square root of areas under the power spectrum. In this study, heart rate variability was expressed as total (0.01–1.00 Hz), low (0.04–0.15 Hz), and high (0.15–0.40 Hz) frequency components. Mean heart rate was also calculated from the 24 hour Holter tapes.

MEASUREMENTS OF THE QT INTERVAL

On each patient the QT interval was measured from electrocardiographic strips that were selected from 24 hour Holter tapes at one hour intervals. The electrocardiograms were then enlarged ×2 by photocopying. The enlarging precision of the photocopier was confirmed by the calibration signal on the electrocardiograms. The QRST complex

chosen for measurement of the QT interval was at least three normal beats after, and not preceding any ventricular ectopic beats.

The QT interval was defined as the interval between the onset of the QRS complex and the end of the T wave. The end of the T wave was defined as the intersection point of the isoelectric line and the tangent line of the maximal downslope of the T wave.⁵ All QT intervals were measured on channel one (the modified V₅ lead) as the T wave on channel two was sometimes of low amplitude and difficult to measure accurately. Three values of the QT interval were measured in each subject. Mean, minimal, and maximal QT intervals were the mean, the shortest, and the longest values of the 24 QT intervals measured throughout the 24 hour period at one hour intervals.

STATISTICAL ANALYSIS

Unpaired Student's *t* test, χ^2 test, and multiple variance correlation and regression were used as appropriate. Analysis of covariance (with age as a covariate) was used for comparing the heart rate variability measurements to adjust for the influence of age.^{6,7} The differences in the slopes of regression lines were tested by the method of Armitage and Berry.⁸ All data were expressed as mean (SD). A *p* value of <0.05 was considered statistically significant.

Results

There was no difference in mean heart rate between groups I and II (70 (9) *v* 72 (13) beats/min, NS).

HEART RATE VARIABILITY

Table 1 shows that there were no significant differences in the low and total frequency components of heart rate variability between group I and group II. The high frequency component of heart rate variability was, however, significantly lower in group II than in group I (16 (8) *v* 21 (12) ms, *p* < 0.05). There was also no difference in any of the three frequency components of heart rate variability between groups II_a and II_b.

QT INTERVAL

Table 2 shows QT intervals expressed as both absolute and corrected values including the mean (SD), maximal and minimal values, and their differences. The corrected QT

Table 1 Heart rate variability and mean heart rate in patients with NHVT and normal subjects

Groups	I	II	II _a	II _b
No	20	27	12	15
Mean heart rate (beats/min)	70 (9)	72 (13)	78 (10)	69 (14)
Heart rate variability components:				
Total frequency (ms)	55 (22)	47 (19)	42 (19)	52 (19)
Low frequency (ms)	36 (15)	32 (14)	28 (15)	35 (14)
High frequency (ms)	21 (12)	16 (8)*	14 (8)	17 (8)

**p* < 0.05. Values are expressed as mean (SD).

Table 2 QT intervals (mean (SD) seconds) in patient with NHVT and normal subjects

Groups	I	II	II _c	II _n
Absolute values:				
Mean	0.37 (0.03)	0.37 (0.10)	0.38 (0.06)	0.35 (0.10)
SD*	0.03 (0.01)	0.03 (0.01)	0.03 (0.01)	0.03 (0.01)
Maximum	0.42 (0.05)	0.42 (0.05)	0.43 (0.06)	0.42 (0.04)
Minimum	0.33 (0.03)	0.33 (0.04)	0.33 (0.04)	0.32 (0.04)
Range†	0.09 (0.03)	0.10 (0.03)	0.10 (0.03)	0.10 (0.03)
Corrected values:				
Mean	0.42 (0.02)	0.42 (0.02)	0.43 (0.03)	0.42 (0.02)
SD*	0.04 (0.06)	0.02 (0.01)	0.03 (0.01)	0.02 (0.01)
Maximum	0.47 (0.04)	0.47 (0.04)	0.49 (0.03)	0.45 (0.03)
Minimum	0.37 (0.02)	0.38 (0.03)	0.38 (0.04)	0.38 (0.03)
Range†	0.10 (0.03)	0.10 (0.08)	0.11 (0.04)	0.10 (0.10)

*Standard deviation about the mean of hourly QT interval over 24 hours.
†Difference between the maximum and the minimum of QT intervals.

interval (QT_c) was calculated by dividing the measured QT interval by the square root of the preceding RR interval using Bazett's formula (QT_c = QT/√RR, in seconds). None of the QT intervals and their corrected values differed significantly between group I and group II nor between group II_c and group II_n.

CORRELATIONS BETWEEN QT INTERVALS AND HEART RATE VARIABILITY
There was a statistically significant correlation between the spectral values of heart rate variability and the mean, maximal, and minimal values of QT intervals in group I, whereas this relation was not found in group II (table 3). The slope of the regression lines between the minimal QT interval and the high frequency component of heart rate variability was significantly altered (−1.2536 *v* 1.6313, *p* < 0.01) in patients with NHVT compared with normal subjects (fig).

Discussion
Idiopathic VT occurs in a small but important subset of patients without overt heart disease.^{1,2} Most of these patients have a good prognosis,⁹ but sudden cardiac death may occur.¹⁰ Although there have been many reports concerning NHVT,¹ its mechanism remains uncertain^{1,2} and the condition has been considered as a primary electrical disease.¹
Heart rate variability has been used as a measure of the effect of the autonomic nervous system on the integrity of cardiovascular activity in many clinical entities including sudden cardiac death¹¹ and cardiac arrhythmias.^{12,13} Decreased heart rate variability has

Table 3 Correlation coefficients between QT intervals and spectral heart rate variability

QT intervals	Frequency components of heart rate variability		
	Total	Low	High
Mean:			
Group I	0.60**	0.56**	0.58**
Group II	−0.09	−0.11	−0.13
Maximum:			
Group I	0.61**	0.59**	0.57**
Group II	0.02	−0.01	0.05
Minimum:			
Group I	0.67***	0.60***	0.71**
Group II	−0.23	−0.27	−0.28

** *p* < 0.01; ****p* < 0.001.

Regression lines between the high frequency (HF) component of heart rate variability (HRV) and minimal QT interval in patients with ventricular tachycardia associated with clinically normal hearts (NHVT) and in controls (C). The slopes are significantly different (*p* < 0.01).

been shown to exist in patients with chronic heart failure⁸ and to correlate with an increased mortality in patients recovering from myocardial infarction.¹⁴ It has been assumed that the low frequency component of heart rate variability in the frequency domain provides a measure of predominantly sympathetic activity with some influence from vagal activity, whereas the high frequency component relates almost exclusively to vagal modulation.^{15–18}

Our results showed that the high frequency component of heart rate variability was significantly decreased in patients with NHVT, suggesting impaired cardiac efferent vagal activity. We have previously shown an impaired sympathovagal balance in a smaller number of patients with NHVT from the same group examined in the present study.⁴ Heart rate variability has been reported by several authors to decrease with age in normal subjects.^{6,7} The differences in heart rate variability in our study, however, were not attributable to difference in age as analysis of covariance was applied to adjust for the influence of age on heart rate variability. Also, the difference in age was not statistically significant between the groups that have been compared. The role of sympathetic activity in the genesis of arrhythmias has been well studied,^{19,20} but the relation of vagal activity to arrhythmogenesis remains to be fully elucidated. Previous reports suggest that sympathetic activation can trigger malignant arrhythmias, whereas vagal activation may exert a protective effect.^{21–24} Our results indicate that reduced vagal activity may also play an important part in arrhythmogenesis in patients with NHVT.

A prolonged QT interval is associated with an increased risk of sudden cardiac death.²⁵ Ventricular repolarisation is predominantly under β adrenergic control²⁶ and sympathetic stimulation shortens the QT interval.^{27,28} There is evidence of vagal innervation of the ventricle²⁹ and that vagus may also be directly involved in the modulation of the QT interval.^{30–32} There is also evidence that the vagus nerve exerts its effect on the electrophysio-

logical properties of the ventricular myocardium by modifying the effect of sympathetic activity on the normal ventricle.²³⁻³³ The interaction of the two opposing branches of the autonomic nervous system may play a more important part than either one alone in the pathophysiological activities of the heart.³⁴⁻³⁵ Decreased vagal activity may have similar effects on the dispersion of refractoriness as does increased sympathetic activity in the genesis of arrhythmias. In our study, no differences were found in the QT intervals and their corrected values, or mean heart rates between groups I and II, or between groups II_a and II_b. The relation between measures of the QT interval and heart rate variability was significantly altered, however, in patients with NHVT compared with normal subjects (table 3 and fig). Inappropriate modulation of the QT interval by abnormal autonomic activity, which is probably due to impaired vagal activity, might be the explanation for the primary electrical disturbance in patients with NHVT.

One limitation is that the QT interval was measured at one hour intervals instead of on a beat to beat basis. This may reduce the sensitivity and hence the ability to detect an alteration of the QT interval in relation to autonomic tone. In our study, the lack of a relation between QT interval and heart rate variability in patients with NHVT was unlikely to be due to this limitation as there was a statistically significant relation between QT interval and heart rate variability in a smaller number of normal subjects.

We conclude that the high frequency component of heart rate variability is significantly decreased and the relation of the QT interval to heart rate variability is significantly altered in patients with NHVT as compared with normal subjects. These findings suggest that in patients with NHVT abnormal modulation of the QT interval by the autonomic nervous system may play an important part in the arrhythmogenesis, which is probably due to impaired vagal cardiac activity.

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