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Diurnal variation of the QT interval—influence of the autonomic nervous system

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SUMMARY To assess the influence of diurnal changes in the autonomic nervous system on the QT interval, 24 hour dynamic electrocardiographic monitoring was performed in six pacemaker dependent patients with normally innervated hearts, in six cardiac transplant patients with anatomically denervated hearts (but which respond to circulating catecholamines), and in nine diabetic patients with confirmed autonomic neuropathy. QT and RR intervals from hourly intervals were measured and Bazett's formula was used to correct QT intervals during sinus rhythm. All QT intervals were normalised by dividing by the mean QT for the 24 hours in each patient and were expressed as a percentage. There was pronounced diurnal variation of normalised QT in the patients with normally innervated hearts. QT intervals were longer during sleep than during waking hours (06.00 *vs* 18.00 h, 102·5% *vs* 97·8%). Diurnal variation was blunted in the transplant patients (101·3% *vs* 98·1%) and absent in the diabetic patients (100·0% *vs* 100·3%). In the normally innervated patients changes were most pronounced at the time of waking (06.00 *vs* 09.00 h, 102·5% *vs* 95·4%). There was no change in normalised QT in the transplant and diabetic patients at this time. There was no significant difference between normalised QT for the three groups during sleep, but this variable was shorter in innervated patients during waking hours (for example at 10.00 h, innervated 96·5%, transplant 100·7%, diabetic 100·7%). Diurnal changes of the QT interval may be pronounced in the innervated heart and are dependent on both variations in autonomic tone and concentrations of circulating catecholamines. These changes in repolarisation may be related to the reported diurnal pattern of ventricular arrhythmias.

The QT interval on the surface electrocardiogram is an indirect measure of myocardial depolarisation and repolarisation. Abnormalities of the QT interval, which indicate abnormal repolarisation, have been linked with the development of ventricular arrhythmias, prinicipally in the long QT syndromes[1–3] and after myocardial infarction.[4 5] Recently there has been considerable interest in the dynamic nature of the QT interval, both normal and pathological,[6] and in particular it has been suggested that the QT interval may be increased during sleep independently of any changes in heart rate.[7] The possible mechanism of this lengthening remains speculative.

There are pronounced changes in autonomic balance during sleep, with either an increase in parasympathetic tone or a decrease in sympathetic activity or both, depending on the phase of sleep.[8] There is also a diurnal variation in circulating endogenous catecholamines—catecholamine output is lower during the night.[9 10] All of these factors could influence myocardial repolarisation, and thus the QT interval, independently of any changes in heart rate that they may produce.

We have attempted to ascertain whether there is diurnal variation of the QT interval, and by using groups of patients with varying degrees of cardiac denervation to gain insight into the possible autonomic mechanisms involved.

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Patients and methods

PATIENTS

Three groups of patients were investigated.

Group A consisted of six patients with permanent

implanted constant rate ventricular demand pacemakers. Their ages ranged from 62 to 84 (mean 73) years and four were men. All patients were totally pacemaker dependent with no sinus or fusion beats during any electrocardiographic recording. These are patients with normally innervated hearts which respond both to changes in neurally mediated autonomic tone and to circulating catecholamines.

Group B consisted of six orthotopic cardiac transplant recipients. Their ages ranged from 25 to 50 (mean 37) years and all six were men. They were studied 4 to 18 (mean 13) months after operation and at the time of this investigation all patients were completely symptom free with no haematological, biochemical, or electrocardiographic evidence of rejection. All patients were taking prednisolone and azathioprine as routine immunosuppressive treatment. Within 48 hours of the ambulatory monitoring reported below, the patients had undergone electrophysiological evaluation during which various physiological manoeuvres, including carotid sinus massage, the cold pressor test, and the Valsalva manoeuvre had been performed.[11] In no case was there a change in either donor heart rate or any conduction interval, confirming the persistence of functional cardiac denervation. Thus these are patients with anatomically denervated hearts which respond solely to circulating catecholamines.

Group C consisted of nine insulin dependent diabetic patients. Their ages ranged from 32 to 61 (mean 43) years and seven were men. All had two or more of the following symptoms suggestive of autonomic neuropathy—impotence, postural hypotension, diarrhoea, perspiration problems, hypoglycaemia unawareness, and gastric stasis symptoms and all had abnormal cardiovascular reflexes indicating both cardiac parasympathetic and more widespread sympathetic damage. Heart rate response to the Valsalva manoeuvre, to deep breathing, and to standing (for parasympathetic damage) and the blood pressure response to standing and to sustained handgrip (for sympathetic damage) were tested.[12]

All patients in the three groups met the following criteria: *(a)* they were not on medications known to influence the QT interval, *(b)* they had no or very infrequent atrial or ventricular premature beats, and *(c)* in those patients in sinus rhythm (groups B and C), there was no evidence of bundle branch block. Apart from one diabetic patient with known coronary artery disease, no other patient in the three groups had important confirmed ischaemic or structural heart disease.

METHODS

All patients underwent at least 24 hours of continuous ambulatory electrocardiographic monitoring on either four inch reel to reel two channel tape recorders or two channel cassette recorders (groups A and B) or single channel cassette recorders (group C). No attempt was made to control the patient's activities during the 24 hours of monitoring; however, all patients had a conventional daily activity pattern—that is they slept at night and were active during the day. Tracings of approximately 10 QRS complexes were printed out every hour for each patient. The RR and QT intervals for each hour were measured blindly and in random order by two observers, who were unaware of the patient's name and the hour of the day but not, because of the differing recording equipment used and the presence of paced beats, the group. Each observer averaged the results of two or three complexes, and then the results of the two observers were averaged. The QT interval was measured from the beginning of the Q wave to the point at which the T wave returned to the isoelectric line. QT intervals during sinus rhythm were corrected for heart rate by means of Bazett's correction ($QTc = QT/RR^{0.5}$, with the RR interval expressed in seconds).[13] To overcome any bias engendered by the longer measured QT intervals of the ventricular paced complexes (that is because a similar percentage change would produce a greater absolute change), all QT intervals were normalised by dividing by the mean QT interval for the 24 hours in each patient and were expressed as a percentage.

STATISTICAL ANALYSIS

All values are quoted as the means and one standard deviation. We compared data by Student's two tailed *t* test for paired and non-paired data. Differences of $p < 0.05$ were regarded as significant.

Results

Group A—All patients had multiprogrammable ventricular pacemakers (Medtronic 5985) which were programmed to the same pacing rate (70 beats per minute) at the time of this study. There was a pronounced diurnal variation in the normalised QT interval over the 24 hours, with significantly longer QT intervals during sleep than during waking hours (see Table and Fig. 1) (for example 06.00 h *vs* 18.00 h, $p < 0.01$; 05.00 h *vs* 17.00 h, $p < 0.01$). The QT interval tended to lengthen during the hours of sleep with the longest intervals being recorded at 05.00 h. The biggest changes occurred at the time of wakening. The QT interval shortened from 103·4% at 05.00 h to 95·4% at 09.00 h ($p < 0.001$). The mean measured QT interval for this group was 461 ms, and this shortening therefore represents, in absolute

Table *Normalised QT intervals for the three groups over the 24 hour period*

Time (h)	*Group A (V paced)*	*Group B (transplants)*	*Group C (diabetics)*
13.00	95·0	99·8	98·7
14.00	95·0	98·1	99·9
15.00	95·7	99·2	100·4
16.00	96·8	98·9	99·7
17.00	98·1	98·5	99·8
18.00	97·8	98·1	100·3
19.00	98·7	98·1	100·0
20.00	100·0	98·3	100·9
21.00	97·8	97·1	99·5
22.00	97·9	99·3	100·6
23.00	100·0	98·5	99·5
24.00	101·9	100·5	100·4
01.00	101·2	101·3	99·6
02.00	101·2	101·4	100·2
03.00	101·1	101·2	99·9
04.00	102·3	100·6	100·1
05.00	103·4	101·5	100·5
(05.30)	(103·0)	—	—
06.00	102·5	101·3	100·0
(06.30)	(101·3)	—	—
07.00	101·2	102·4	99·7
(07.30)	(99·1)	—	—
08.00	95·9	100·6	99·4
09.00	95·4	102·2	100·3
10.00	96·5	100·7	100·7
11.00	95·4	101·9	98·4
12.00	95·7	100·5	100·3

All values are in percentages. V, ventricular.

terms, a change of 37 ms in the measured QT. The shortening was maintained during the active hours of the day and then the QT interval gradually lengthened during the evening. The average difference between definite sleeping hours (01.00–06.00 h) and definite waking hours (10.00–22.00 h) was 5·0% or 23 ms in absolute terms. Having analysed the data as indicated in the methods section, we retrospectively analysed the intervening 30 minute intervals at the time of the most rapid change and these are included in the Table in parentheses.

Group B—There was little variation in mean hourly heart rate over the 24 hours in group B patients—the maximum to minimum heart rate difference being 17·2 beats per minute (Fig. 2). The greatest difference in maximum and minimum heart rate in any one of the patients was 29 beats per minute. Diurnal variation of the QT interval was present but was considerably blunted with only slightly longer QT intervals during sleep than during waking hours (Table and Fig. 1). At no time did the difference between a sleeping hour and a waking hour achieve statistical significance. In contrast with the normally innervated patients (group A) there was no change in the QT interval at the time of waking. The average difference between definite sleeping and waking hours was 2·1% (in absolute terms 9 ms).

Group C—As with group B patients there was little variation in mean hourly heart rate, maximum to minimum heart rate difference being 17·5 beats per minute (Fig. 2). The greatest difference in maximum and minimum heart rate in any one patient was 37 beats per minute. Diurnal variation of the QT interval was completely absent with no difference between sleeping and waking hours (Table and Fig. 1). The average difference between definite sleeping and waking hours was 0·11% (in absolute terms 0·5 ms).

Figure 1 shows that there are no significant differences in normalised QT interval among the three groups during the hours of sleep, although there was some lengthening in the innervated patients before waking. The QT interval, however,

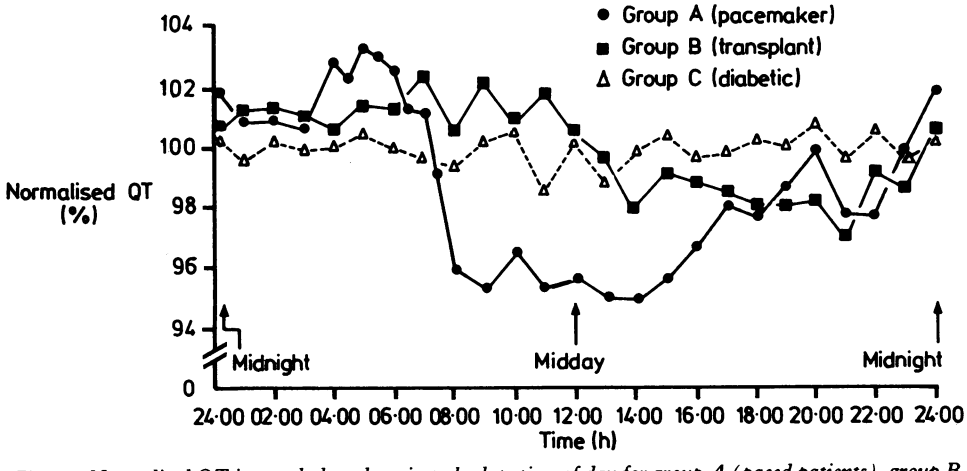

Fig. 1 *Normalised QT interval plotted against absolute time of day for group A (paced patients), group B (transplant patients), and group C (diabetic patients).*

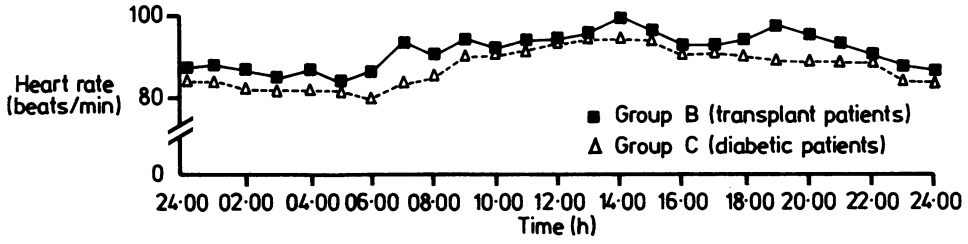

Fig. 2 *Mean hourly heart rate plotted against absolute time of day for transplant patients and diabetic patients.*

was significantly shorter during waking hours in those with innervated hearts (for example at 10.00 h group A, 96·5%; group B, 100·7%; group C, 100·7% ($p < 0·01$)). The interobserver differences in measured QT were small—for example for all measurements in group A patients the differences ranged from 0 to 20 (mean 2·3 ms).

Discussion

These data confirm the previous work of Browne *et al* indicating that the QT interval is prolonged during sleep.[7] The methods and patient groups that we studied meant that we were able to gain some insight into the possible physiological mechanisms. Browne *et al* suggested that this prolongation may reflect either increased vagal tone or sympathetic withdrawal, in other words a net increase in parasympathetic tone. They made no mention of the possible role of circulating catecholamines, which are known to influence the QT interval.[14] Also because they compared RR intervals of identical duration during wakefulness and sleep, they were not able to comment on the possible time course of events.

When the effect of an intervention on the QT interval is assessed it is usual to correct for changes in heart rate.[13 15] When there is a considerable change in heart rate, however, the application of a correction factor such as Bazett's formula may lead to spurious and misleading results.[16-18] Bazett's formula may only be accurate when the heart rate is between 50 and 115 beats per minute,[16] and more recently some workers have suggested an even smaller range of rates (RR intervals, 700 ms to 1050 ms).[7] To circumvent this problem Milne *et al* suggested that the effects of an intervention on the QT interval should be assessed at identical atrial[17] or ventricular[19] paced rates. In this study we assessed patients at ventricular paced rates. It could be argued that the absence of changes in the transplant and diabetic patients is related to errors engendered by the use of Bazett's correction in these groups. Figure 2, however, shows that the variation in heart rate in these two groups is extremely small and within the range over which Bazett's correction is probably valid.

For a long time it has been accepted that the heart rate slows during sleep and that this is related to considerable diurnal changes in the autonomic nervous system.[20 21] It was initially felt that this fall in heart rate during sleep was entirely related to an increase in parasympathetic tone.[20] Samaan in 1934, however, suggested that there was an additional decrease in sympathetic activity.[22] More recent work, in which different kinds and degrees of heart denervation were studied, has also indicated that both an increase in vagal tone and decreased sympathetic discharge occur, depending on the phase of sleep.[8] After complete cardiac denervation by combined bilateral vagotomy and stellectomy the decrease in heart rate during sleep, although markedly reduced, still occurred.[8] There is also a circadian variation in concentrations of circulating endogenous catecholamines.[10] In the study by Barnes *et al*, the highest values of plasma adrenaline were recorded at 16.00 h and the lowest values at 04.00 h.[10]

All of these autonomic factors, as well as affecting heart rate, have been shown to influence the QT interval independent of any changes in rate. Assessment of the QT interval by the pacing technique mentioned previously has shown that loss of parasympathetic tone induced by atropine shortens the QT interval[18 23] and ventricular effective refractory period[24] and that loss of sympathetic tone induced by propranolol either has no effect[18 23] or may tend to prolong[17] the QT interval and ventricular refractory periods.[24] Thus both the increase in parasympathetic tone and decrease in sympathetic activity occurring during sleep[8] will tend to lengthen the QT interval independently of the slowing in heart rate. Similarly the infusion of catecholamines has been shown to shorten the QT interval, again independently of rate changes,[14] suggesting that the low concentrations encountered during sleep will lead to a relative lengthening of this interval.

Thus the autonomic changes occurring during sleep will all tend to lengthen the QT interval. That

this actually occurs is illustrated by the normally innervated patients in group A who had significantly longer QT intervals during sleep than during waking hours. The QT interval tended to lengthen during the hours of sleep, with the longest intervals being seen at 05.00 h when the concentration of circulating catecholamines is at its lowest[10] and when previous studies have documented that the heart rate is slowest.[21 25] The QT interval shortened rapidly during the hours of waking, during which plasma adrenaline concentrations are rapidly rising,[10] and there is inhibition of the parasympathetic cardioinhibitory centre at the time of arousal.[8] Obviously other factors such as physical exertion and meals may have influenced the QT interval during waking hours but these activities probably only account for a minor portion of the data collected for each patient and are presumably similar in the three groups.

Diurnal variation of the QT interval was still apparent in the transplant patients, with longer QT intervals during sleep, although the changes were not significant and were considerably blunted compared with those in the innervated group. The transplanted heart seems to remain functionally and anatomically denervated indefinitely,[26 27] although it responds appropriately to catecholamines.[28] Thus any changes observed in the QT interval, corrected for heart rate, must be related to changes in the concentration of circulating catecholamines. Although the QT interval in this group tended to lengthen towards the end of sleep, it is interesting that the longest QT interval was delayed by approximately two hours compared with that in innervated patients and did not coincide with the time at which circulating catecholamines might be expected to be at their lowest concentration.[10] The reason for this apparent discrepancy is unclear.

In the diabetic patients, who had proven autonomic neuropathy, there was no diurnal variation of the QT interval. These patients with advanced, symptomatic cardiac parasympathetic and more widespread sympathetic damage do not respond to neurally mediated changes in autonomic tone.[12] It has also been shown that plasma catecholamine concentration is reduced in long term diabetics with signs of somatic neuropathy and indeed that there is a close correlation between this reduction in plasma catecholamine concentration and the degree of autonomic neuropathy,[29] which was quite severe in the group C patients. Long term diabetic patients may also show an abnormally blunted plasma catecholamines response to manoeuvres such as standing.[29] Unfortunately data on the diurnal variation of catecholamines in diabetics with proven neuropathy are not available.

It is apparent from these data that there is diurnal variation of the QT interval in the normally innervated heart which may be quite pronounced. This variation appears to be dependent, perhaps to an equal extent, on changes in both neurally mediated autonomic tone (presumably predominantly heightened parasympathetic tone during sleep) and on the circadian variation in circulating catecholamines. Several studies have shown that sleep is associated with a decrease in both the frequency and severity of ventricular arrhythmias both in patients with ischaemic heart disease and in healthy subjects.[30-32] It is therefore interesting to note that in the innervated patients (group A) the longest QT intervals, at a constant heart rate, occurred at the same stage of sleep that previous studies have documented the lowest frequency of arrhythmias.[32] It is tempting to suggest that those autonomic factors which lengthen the QT interval may, independently of any effect they may have on heart rate, reduce the temporal dispersion of refractoriness and thus the tendency for arrhythmias.

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References

1 Jervell A, Lange-Nielson F. Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval, and sudden death. *Am Heart J* 1957; **54:** 59–68.
2 Romano C, Gemme G, Pongiglione R. Aritmie cardiache rare dell' etá pediatrica. II. Accessi sincopali per fibillazione ventricolare parossistica. *Clin Paediat* 1963; **45:** 656–83.
3 Ward OC. A new familial cardiac syndrome in children. *J Irish Med Assoc* 1964; **54:** 103–6.
4 Schwartz PJ, Wolf S. QT interval prolongation as predictor of sudden death in patients with myocardial infarction. *Circulation* 1978; **57:** 1074–7.
5 Ahnve S, Helmers C, Lundman T, Rehnqvist N, Sjogren A. QTc intervals in acute myocardial infarction: first-year prognostic implications. *Clin Cardiol* 1980; **3:** 303–8.
6 Butrous GS, Ward DE, Camm AJ. Revelation of latent cases of long QT syndrome by rapid autonomic tone modulation [Abstract]. *Br Heart J* 1984; **51:** 694.
7 Browne KF, Prystowsky E, Heger JJ, Chilson DA, Zipes DP. Prolongation of the Q-T interval in man during sleep. *Am J Cardiol* 1983; **52:** 55–9.
8 Baust W, Bohnert B. The regulation of heart rate during sleep. *Exp Brain Res* 1969; **7:** 169–80.
9 Townshend MM, Smith AJ. Factors influencing the

urinary excretion of free catecholamines in man. *Clin Sci* 1973; **44:** 253–65.
10 Barnes P, Fitzgerald G, Brown M, Dollery C. Nocturnal asthma and changes in circulating epinephrine, histamine, and cortisol. *N Engl J Med* 1980; **303:** 263–7.
11 Bexton RS, Nathan AW, Hellestrand KJ, *et al*. The electrophysiologic characteristics of the transplanted human heart. *Am Heart J* 1984; **107:** 1–7.
12 Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. *Br Med J* 1982; **285:** 916–8.
13 Bazett HC. An analysis of the time-relations of electrocardiograms. *Heart* 1920; **7:** 353–70.
14 Abildskov JA. Adrenergic effects on the QT interval of the electrocardiogram. *Am Heart J* 1976; **92:** 210–6.
15 Ashman R. The normal duration of the Q-T interval. *Am Heart J* 1942; **23:** 522–34.
16 Simonsen E, Cady LD, Woodbury M. The normal Q-T interval. *Am Heart J* 1962; **63:** 747–53.
17 Milne JR, Camm AJ, Ward DE, Spurrell RAJ. Effect of intravenous propranolol on QT interval. A new method of assessment. *Br Heart J* 1980; **43:** 1–6.
18 Browne KF, Zipes DP, Heger JJ, Prystowsky EN. Influence of the autonomic nervous system on the Q-T interval in man. *Am J Cardiol* 1982; **50:** 1099–103.
19 Milne JR, Hellestrand KJ, Bexton RS, Burnett PJ, Debbas NMG, Camm AJ. Class I antiarrhythmic drugs—characteristic electrocardiographic differences when assessed by atrial and ventricular pacing. *Eur Heart J* 1984; **5:** 99–107.
20 Sutherland GA, McMichael J. The pulse-rate and range in health and disease during childhood. *Q J Med* 1929; **22:** 519–29.
21 Boas EP, Weiss MM. The heart rate during sleep as determined by the cardiotachometer. Its clinical significance. *JAMA* 1929; **92:** 2162–8.
22 Samaan A. La fréquence cardiaque du chien en différentes conditions expérimentales d' activité et de repos. *C R Soc Biol (Paris)* 1934; **115:** 1383–8.
23 Tonkin AM, Tornos P, Heddle WF, Rapp H. Autonomic effects on the human cardiac conduction system. Evaluation by intracardiac electrocardiography and programmed stimulation techniques. *Br Heart J* 1980; **44:** 168–74.
24 Prystowsky EN, Jackman WM, Rinkenberger RL, Heger JJ, Zipes DP. Effect of autonomic blockade on ventricular refractoriness and atrioventricular nodal conduction in humans. Evidence supporting a direct cholinergic action on ventricular muscle refractoriness. *Circ Res* 1981; **49:** 511–8.
25 Tzivoni D, Stern S. Electrocardiographic pattern during sleep in healthy subjects and in patients with ischemic heart disease. *J Electrocardiol* 1973; **6:** 225–9.
26 Stinson EB, Griepp RB, Schroeder JS, Dong E Jr, Shumway NE. Hemodynamic observations one and two years after cardiac transplantation in man. *Circulation* 1972; **45:** 1183–94.
27 Mason JW, Harrison DC. Electrophysiology and electropharmacology of the transplanted human heart. In: Narula OS, ed. *Cardiac arrhythmias: electrophysiology, diagnosis and management*. Baltimore: Williams and Wilkins, 1979: 66–81.
28 Cannom DS, Rider AK, Stinson EB, Harrison DC. Electrophysiologic studies in the denervated transplanted human heart. II. Response to norepinephrine, isoproterenol and propranolol. *Am J Cardiol* 1975; **36:** 859–66.
29 Christensen NJ. Plasma catecholamines in long-term diabetics with and without neuropathy and in hypophysectomized subjects. *J Clin Invest* 1972; **51:** 779–87.
30 Lown B, Tykocinski M, Garfein A, Brooks P. Sleep and ventricular premature beats. *Circulation* 1973; **48:** 691–701.
31 Lown B, Calvert AF, Armington R, Ryan M. Monitoring for serious arrhythmias and high risk of sudden death. *Circulation* 1975; **51/52** (suppl III): III-189-98.
32 Pickering TG, Johnston J, Honour AJ. Comparison of the effects of sleep, exercise and autonomic drugs on ventricular extrasystoles, using ambulatory monitoring of electrocardiogram and electroencephalogram. *Am J Med* 1978; **65:** 575–83.