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Electrocardiographic Repolarization During Stress From Awakening on Alarm Call

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Objectives. **The present study aimed to characterize the electrocardiographic features of cardiac repolarization during an arousal reaction in healthy subjects.**

Background. **Electrocardiographic ST segments and T waves may indicate the activity of cardiac autonomic nervous control. Abnormal dynamics of repolarization are considered to reveal susceptibility to cardiac arrhythmias. Responses in normal subjects may help to understand the effects on patients' arrhythmias.**

Methods. **Ambulatory electrocardiography was performed in 30 healthy physicians during emergency calls while they were on duty in the hospital. Samples were taken before and during the 1st 30 s after the calls. Polarity of the T wave and ST segment depression were determined. The QT interval and the cardiac cycle length (CL) were measured, and their relation (QT/CL slope) was calculated. For comparison, the QT interval was also measured in stable conditions at specified heart rates of 60 to 110 beats/min.**

Results. **During arousal, the T wave was inverted in 19 subjects (63%) and the ST segment depressed ≥0.1 mV in 10 (33%). The proportional duration of the terminal T wave also varied. The time course of these alterations followed the change in heart rate. During the strongest arousal reaction, the heart rate increased from 55 ± 7 to 112 ± 18 beats/min (mean ± SD) and reached maximum at 17 s on average. The QT interval shortened only slightly and was on average 59 to 67 ms longer ($p < 0.001$) than that at similar heart rates during stable conditions. The QT/CL slope was almost horizontal, 0.085 ± 0.061, during arousal and much steeper, 0.168 ± 0.055 ($p < 0.001$), during stable conditions.**

Conclusions. **Derangements in the T wave and ST segment as signs of sympathetic overactivity are common during arousal and are associated with marked inertia in QT interval adaptation. These modifications of ventricular repolarization may mediate the generation of stress-provoked arrhythmias in electrically unstable hearts.**

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Ventricular repolarization is affected by the autonomic nervous system, and this relation is reflected in the morphology of the electrocardiographic (ECG) ST segment and T wave (1–5), as well as in the length of the QT interval (6,7). The duration of the ventricular action potential and the QT interval depend on cardiac cycle length (CL) rather predictably during stable conditions (8), but it shows an inconsistent relation during maneuvers that rapidly shift heart rate and autonomic nervous tone (9–12). These include the Valsalva maneuver, cold pressor test, eliciting of the dive reflex, mental stress of performing arithmetic task and rapid onset of exercise (13–16). Repolarization is a determinant of ventricular excitability and is fundamentally involved in arrhythmogenesis.

Sudden stress is known to evoke life-threatening arrhythmias in subjects who have certain predisposing conditions (17–19), suggesting that strong autonomic nervous influences can abruptly render the heart vulnerable. The present study examined how ventricular repolarization is influenced by an arousal reaction of awakening to a stressful alarm call.

Methods

Subjects and test situation. The subjects were 30 physicians, 9 women and 21 men, and their ages ranged from 29 to 52 years (mean ± SD 35 ± 7 years). Their work experience ranged from 2 to 8 years (median 4). None had any history of cardiac disease or diabetes or used any drugs that could influence heart rhythm. Cardiac Doppler ultrasonography yielded normal results in subjects examined because of observed ST segment depression.

Ambulatory ECGs were recorded when the physicians worked on duty in a university hospital from 3 PM to 8 AM the next day. They could rest and sleep at night but frequently received emergency phone calls from the patient wards. A log was kept of the call times.

ECG determinations. Two electrograms resembling leads V_1 and V_5 were recorded and analyzed with an ambulatory ECG system (Marquette Electronics, Inc.). Detection of QRS complexes and rhythm analysis were performed automatically, and the results edited by one of the investigators. Arousal periods during rest or sleep were identified by using log times

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Abbreviations and Acronyms

ANOVA = analysis of variance
CL = cardiac cycle length
ECG = electrocardiogram, electrocardiographic
QT/CL = QT interval/cardiac cycle length slope

and looking for a sudden increase in rate and movement artifacts.

Analysis was started before arousal and continued until the heart rate decreased again. ECG strips were sampled 30 and 5 s before and 5, 10, 20 and 30 s after the first evidence of arousal. Samples were also taken at the maximal heart rate, T wave inversion and ST segment depression. For comparison, samples were collected at stable heart rates of 60, 70, 80, 90, 100 and 110 beats/min between 4 and 8 PM. To be considered representative, the rate was required to stay at the specified level (with an accuracy level of ≤5 beats/min) for ≥1 min. For diurnal variation, samples were taken between 4 and 8 PM and between 2 and 5 AM during slow heart rates.

T wave morphology was analyzed from the V_5-like channel, and was classified as positive, negative, biphasic or isoelectric. Initially, the T wave was positive in the sitting and standing positions in each subject. T wave amplitude was measured as maximal deviation from the PR line. The ST segment level was measured 60 ms after the J point from the V_5-like channel. Planar, downsloping and slowly ascending ST segment depressions ≥0.1 mV were recognized. No subject had any polarity change or conduction anomaly in the QRS complex.

Intervals were analyzed with use of the V_5-like channel at a paper speed of 25 mm/s by one of the investigators using the arousal episode with the greatest change in heart rate. The QT interval was measured from the onset of the QRS complex to the end of the T wave, and the QT apex interval to the peak of the T wave, whether positive or negative (20). Samples with isoelectric or biphasic T waves were excluded. QT and cardiac cycle intervals were measured from the same three consecutive heartbeats and the readings were averaged. The terminal part of repolarization—that is, the terminal T wave—was obtained by subtraction (QT interval − QT apex interval). Its proportion was calculated as (QT interval − QT apex interval)/QT interval.

QT interval dynamics and heart rate variability. The relation of the QT interval and CL was determined by using linear regression analysis and is presented as the QT/CL slope. This value was created separately for samples obtained during arousal and during stable conditions. To demonstrate dissimilarity of QT interval in different physiologic states, QT intervals were interpolated to any targeted heart rate by adapting the formula

$$QT_i = QT_m + Slope \times (CL_m - CL_t),$$

where QT = QT interval, i = interpolated; m = measured; t = targeted; and Slope = QT/CL slope of either an arousal or stable condition.

Table 1. Heart Rate and T Wave During Arousal*

	Mean ± SD	Range
Heart rate (beats/min)		
Before arousal	55 ± 7	40–68
Highest heart rate	112 ± 18	80–159
Rate 30 s after arousal	97 ± 24	51–158
Time of ECG events (s)		
Time to maximal rate	17 ± 6	3–27
Time to peak negative T wave (n = 18)	18 ± 5	13–33
Duration of high heart rate†	21 ± 11	6–40
Duration of T wave inversion (n = 18)	6 ± 9	5–35

*n = 30 unless otherwise indicated. †Heart rate ≥80% of maximum. ECG = electrocardiographic.

Heart rate variability was analyzed with an amplitude spectral method by using software from Marquette Electronics. The QRS complex classification was edited by the operator and arrhythmic periods were rejected before analysis. The determined bands were high frequency (0.15 to 0.40 Hz) and low frequency (0.04 to 0.15 Hz), and their ratio was calculated. Data were averaged over 24 h.

For statistical evaluation, analysis of variance (ANOVA) with repeated measures and the Student *t* test were used to compare separate periods and subgroups, with Bonferroni correction for multiple comparisons. Linear regression analysis was used to create QT/CL slopes and to examine correlations. The chi-square test was used to examine incidence rates in subgroups. Parametric values are expressed as mean value ± SD. A p value < 0.05 was taken as statistically significant.

The study was approved by the institutional ethical review board.

Results

Heart rate, T wave and ST segment. The subjects were aroused from rest or sleep by a median of 4 (range 1 to 8) alarm calls between noon and 6 AM. Heart rate increased from 56 ± 8 to 99 ± 20 beats/min during these events. The T wave became negative in 38% of all events. Nineteen subjects (63%) had at least one episode of T wave inversion, which was equally common in women and men (7 of 9 and 12 of 21, respectively, p = NS). ST segment depression ≥0.1 mV occurred in 10% of the events and at least once in 10 subjects (33%), of whom 4 had 0.2 mV depression. ST segment depression was more common in women than in men, occurring in 6 of 9 and 4 of 21, respectively ($p < 0.01$). Each subject with ST segment depression also had T wave inversion. The increase in heart rate was greater in subjects with T wave inversion ($p < 0.05$) and ST segment depression ($p < 0.001$) than in those without such findings. Heart rate variability indexes were not correlated with T wave shape or ST segment depression.

Episode with highest heart rate. Heart rate rose from 54 ± 7 to 112 ± 18 beats/min during the arousal episode associated with the greatest increase in heart rate. The maximal rate was reached within 17 s on average (Table 1). The T wave became

Table 2. T Wave Configuration Before and During Arousal

	Before Arousal	During Arousal				
		5 s	10 s	17 s*	20 s	30 s
T wave polarity (n)						
Positive	30	29	19	15	16	23
Negative	0	0	10	11	12	4
Biphasic	0	0	1	3	2	2
Isoelectric	0	1	0	1	0	1
Terminal T wave†						
Duration (ms)	90 ± 12	82 ± 16	76 ± 20	74 ± 22	78 ± 25	87 ± 24
Proportion	0.21	0.19	0.18	0.18	0.19	0.22

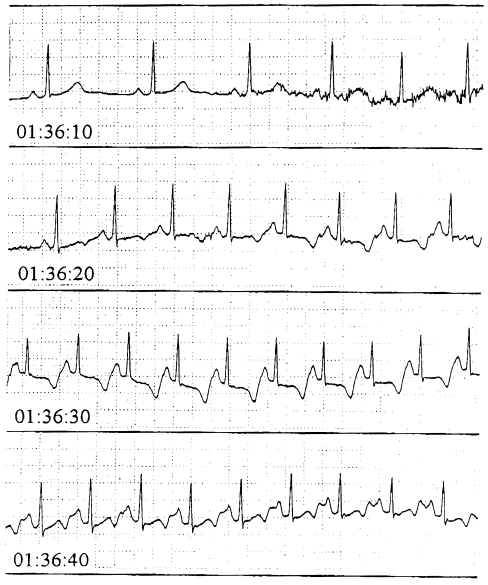
*At peak heart rate, coinciding at 17 s on average. †Definition in text; n = 24 subjects. Respective heart rates and QT intervals for these 24 subjects are indicated in Table 3. Data presented are mean values ± SD (duration) or mean (proportion).

negative in 18 subjects, and ST segment depression occurred in 8 subjects.

The duration of T wave inversion and the time to reach peak negative amplitude are indicated in Table 1. The maximal negative amplitude ranged from 0.1 to 0.6 mV (mean 0.4 ± 0.2 mV). Table 2 indicates the frequency of alterations in T wave configuration. The T wave was negative in 18 subjects and isoelectric or biphasic in 6 at some of the measurement points. Alterations appeared commonly within 10 s and had disappeared in many subjects by 30 s. Figure 1 shows an example of T wave and ST segment responses.

QT intervals during arousal were of equal length in subjects with and without T wave inversion. The terminal T wave shortened both absolutely and relatively during increased heart rate, then lengthened again after the decline in rate (Table 2) ($p < 0.01$ by ANOVA for the proportional value).

Figure 1. ECG tracings obtained from a 31-year old woman during arousal. The four strips recorded within 10-s intervals first show signs of reaction, then inversion of the T wave, ST segment depression of 0.2 mV and, in the last strip, biphasic T waves.



QT interval duration. The effect of arousal on QT interval duration was examined from the episode associated with the highest heart rate. Measurements were obtained from 24 subjects with a recognizable T wave termination at each measurement point. QT intervals with respective heart rates during arousal are presented in Table 3, which also shows QT intervals at similar heart rates during stable conditions. During arousal, shortening of the QT interval was markedly delayed (Fig. 2 and 3). At their longest at 10 s, QT intervals were on average 67 ms longer than during stable conditions (Table 3). The average QT interval during the entire arousal period remained ~50 ms longer than the interval during stable conditions if the preexisting 18-ms difference before the arousal is subtracted. QT intervals differed statistically ($p < 0.001$) at all measurement points.

QT/CL slope. QT/CL slopes were calculated in 24 subjects who had complete QT interval measurements during arousal (Table 4). During stable conditions the slope was 0.168 ± 0.055; during arousal, it was 0.085 ± 0.061 ($p < 0.001$) when calculated by using values obtained up to peak heart rate, and even less when the observation period was shortened (Table 4). During the decline in heart rate, from the time of peak rate to 30 s, the QT/CL relation varied and showed poor correlation

Table 3. Measured and Interpolated QT Intervals During Arousal

	Heart Rate (beats/min)	QT Interval (ms)		
		Measured	Expected*	Difference†
Before arousal				
−30 s	55 ± 7	428 ± 28	410 ± 27	+18
−5 s	55 ± 7	428 ± 28	410 ± 27	+18
During arousal				
5 s	92 ± 12	397 ± 23	334 ± 16	+63
10 s	100 ± 15	390 ± 40	323 ± 18	+67
17 s‡	112 ± 18	362 ± 41	303 ± 16	+59
20 s	104 ± 20	365 ± 37	315 ± 15	+40
30 s	97 ± 24	352 ± 40	327 ± 15	+25

*Calculated to respective heart rates from the QT interval/cardiac cycle length slope during stable conditions. †Difference between the measured and expected QT intervals. ‡At peak heart rate, coinciding at 17 s on average.

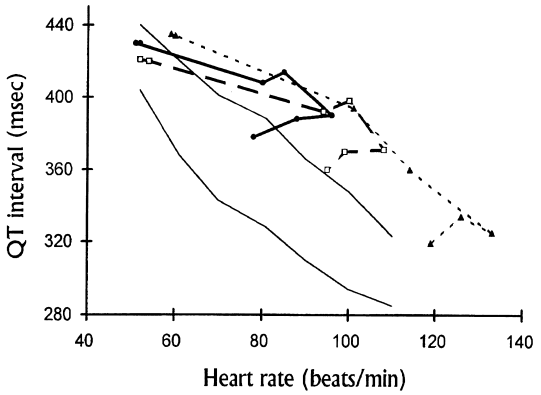


Figure 2. QT intervals and heart rates during arousal in 24 subjects. The subjects are separated into three subgroups according to the highest heart rate achieved: <100 beats/min (**solid line,** n = 8), 100 to 110 beats/min (**dashed line,** n = 8) and >110 beats/min (**dotted line,** n = 8). The lines connect measurement points before and 5, 10, 20 and 30 s after arousal, with the value at the peak heart rate occurring at 17 s on average. The QT interval behaved similarly irrespective of the heart rate eventually achieved. The **two thin lines** represent ±1 SD of the QT intervals measured during stable conditions.

coefficients. Graphic presentation (Fig. 2 and 3) demonstrates a negative trend, that is, leftward inclining QT/CL slopes in that period. The QT apex interval/CL relation during arousal was similar to that of the QT/CL relation (Table 4). Its smaller value is, at least partially, attributable to the relative shortness of the QT apex interval, but it may also reflect different dynamics. A change in the terminal T wave suggests some divergence in the behavior of QT and QT apex intervals.

Corrected QT intervals. QT/CL slopes were used to calculate corrected QT intervals, that is, interpolated to the heart rate of 60/min, in 24 subjects (Table 5). Corrected QT intervals were markedly prolonged during arousal if interpolation was based on the slope obtained during stable conditions. As anticipated, interpolation based on the slope during arousal yielded shorter and less variable values. Bazett's equation

Figure 3. Comparison of QT intervals and heart rates during arousal (**dashed line**) and stable conditions (**solid line**). Data shown are the average values of 24 subjects. The **vertical bars** represent the difference in QT interval (numeric values are given in Table 3).

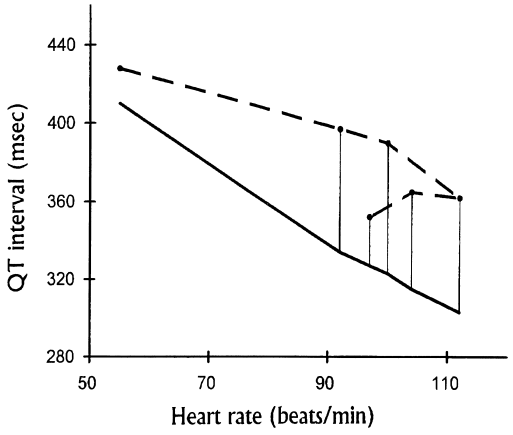


Table 4. Relation of QT Interval and QT Apex Interval to Cardiac Cycle Length

	QT/CL Slope		QT_{apex}/CL Slope	
	Mean ± SD	r*	Mean ± SD	r*
Stable conditions	0.168 ± 0.055	0.94	0.148 ± 0.054	0.92
During arousal				
To peak heart rate	0.085 ± 0.061	0.82	0.063 ± 0.051	0.75
To 10 s	0.068 ± 0.049	0.78	0.049 ± 0.050	0.80

*Group means of regression coefficients for the slopes. CL = cardiac cycle length; QT = QT interval; QT_{apex} = QT apex interval.

produced extraordinarily long QT intervals at high rates (Table 5). Correction of QT apex intervals produced a general pattern that resembled that of QT intervals (data not presented).

QT intervals were measured during the day and at night at mean heart rates of 62 ± 10 and 54 ± 7 beats/min, respectively. Their correction to 60 beats/min using QT/CL slopes during stable conditions produced slightly longer values at night: 404 ± 26 versus 390 ± 24 ms during the day ($p < 0.001$).

Discussion

The present study confirms that alterations in the morphology of the T wave and ST segment commonly occur during arousal from rest or sleep in healthy subjects. These changes coincide with rapid elevation of heart rate and are likely to represent a sudden shift toward sympathetic dominance in the autonomic nervous system. Adaptation of the QT interval to an increased heart rate during arousal shows marked inertia. The mismatch of heart rate and repolarization time and abrupt modification of autonomic control constitute mechanisms that may generate arrhythmias in patients with underlying heart disease.

T wave inversion can be detected during regular daily activity in healthy persons. Its incidence has ranged from 11% to 20% of subjects when analyzed from 24-h ambulatory ECGs

Table 5. Measured and Corrected QT Intervals During Arousal

		Corrected QT (*ms)		
	Measured QT (ms)	Stable	Arousal	Bazett's Equation
Before arousal				
−30 s	428 ± 28	409 ± 28	417 ± 25	408 ± 28
−5 s	428 ± 22	409 ± 25	417 ± 23	407 ± 24
During arousal				
5 s	397 ± 23	454 ± 24	430 ± 21	489 ± 33
10 s	390 ± 40	456 ± 33	428 ± 35	499 ± 41
17 s†	362 ± 41	439 ± 33	406 ± 36	491 ± 39
20 s	365 ± 37	434 ± 26	404 ± 30	475 ± 33
30 s	352 ± 40	411 ± 28	385 ± 30	440 ± 37

*Corrected to heart rate of 60 beats/min using QT/CL slopes obtained during stable conditions, during arousal and using Bazett's equation. †At peak heart rate, coinciding at 17 s on average. n = 24; data are presented as mean value ± SD. Abbreviations as in Table 4.

or when tested in different body positions (2,21). T wave inversion has occurred in 2% to 4% of subjects during hyperventilation or the Valsalva maneuver (1) and in 1 of 80 subjects performing an arithmetic task (21). A pure rate elevation, such as that induced by atrial pacing, does not result in T wave inversion (22). Also ST segment depression has been observed (2,23) infrequently in healthy persons (6% incidence on 24 h ambulatory recording).

Autonomic nervous system modification. T wave inversion and ST segment depression were common, appearing altogether in ~66% of subjects. This finding indicates that healthy subjects exhibit transient repolarization abnormalities even more commonly than previously reported. T wave inversion and ST segment depression appeared rapidly and simultaneously, in contrast to the late development of T wave negativity in myocardial ischemia. Furthermore, the shape of the repolarization wave was modified to express shorter terminal T wave during arousal. The latter may represent disparate changes in action potential duration between ventricular muscle layers (24).

The coincidence of repolarization changes around the maximal heart rate during arousal suggests that these changes were elicited by strong autonomic nervous effects. ST depression is prevalent in patients with neurocirculatory asthenia, and it is attributed to sympathetic overactivity (4,23). However, T wave inversion and ST segment depression were not associated with heart rate variability indexes, suggesting that an individual subject's current—but not predominant—autonomic nervous state determined these changes. Arousal induces ECG changes that mimic those in diseased hearts, thus emphasizing the need for knowledge of physiologic circumstances for proper interpretation of these changes.

QT interval duration. Heart rate, action potential duration and QT interval are closely related (24–26). Rate dependence of the QT interval has been examined by comparing cardiac pacing with physiologic and pharmacologic maneuvers, and pacing during autonomic blockade. Approximately 50% of QT interval shortening during physical activity is caused by a change in heart rate alone (7,10,26). In contrast to sustained physical exercise, which shortens the QT interval in proportion to CL (9,16,27), sudden physical effort diminishes QT interval instantaneously only to a small degree (14,24). Increased heart rate during sympathetic activation by cold pressor test or by injection of isoproterenol is likewise associated with only slight shortening of the QT interval (13), and even lengthening may occur with prompt administration of epinephrine (28). In contrast, increasing the rate by vagal antagonism with atropine shortens the QT interval considerably, which occurs even when heart rate is controlled by pacing (4,8,29). Thus an abrupt sympathetic surge permits the QT interval to remain almost unchanged, whereas sustained high sympathetic tone, vagal withdrawal and adaptation to high rate would shorten it substantially. Therefore the delay in QT interval shortening is consistent with suddenly increased sympathetic activity.

QT/CL relation. Our study compared QT intervals measured during two different physiologic conditions but at the same heart rates, thus avoiding correction algorithms. The QT/CL relation was strikingly dissimilar in the two conditions. The QT/CL slope was small during arousal, diminishing further with shortening during the observation period. The relation disappeared or even reverted during recovery, as suggested by a trend to negative QT/CL slopes after arousal. This finding is consistent with previous demonstration of hysteresis in QT interval adaptation (8,30), although autonomic nervous mechanisms are likely to have been involved, as discussed earlier.

Because variance in heart rate confounds determination of the intrinsic QT interval, various correction formulas have been utilized. The QT/CL relation has been studied not only during rest within groups but, recently, also within individual subjects by using ambulatory electrocardiography (31,32) and exercise testing (33,34). Automated analysis of the QT/CL relation has been adapted to assess repolarization dynamics (31). Kinetics of rate adaptation, hysteresis phenomenon and variable effect of the autonomic nervous system on the QT interval should discourage adherence to a single QT/CL slope index, particularly when attempting to characterize QT interval dynamics in long-term monitoring. Formulas generally utilized to correct the QT interval cannot be applied in altered physiologic states.

Limitations of the study. The corrected QT interval is known (35) to be longer at night than during the day. The present study found a 14-ms diurnal difference, and the measured QT interval before the arousal reaction was 18 ms longer than during stable conditions. Therefore, arousal and stable conditions were not thoroughly comparable. Our methods could not isolate the specific effect of arousal from the effect of sudden heart rate increase; well matched fluctuations in heart rate would not occur during stable physiologic states. The presence of coronary artery disease in our subjects was not ruled out, but because of its low probability in our study subjects, this factor should not confound the overall findings.

Implications. Observations like those in the present study provide reference values that may be useful, for example, in diagnosing the long QT syndrome, in which sudden arousal is known to produce alterations in the T wave and QT interval and ventricular arrhythmias (3,17,18). QT interval shortening during physical exercise depends on genotype in the congenital long QT syndrome (36), but sudden variation is not well described. QT interval duration is associated with life-threatening arrhythmias in acquired heart diseases (37,38) as well, which extends the importance of reliable QT interval analysis beyond the congenital syndrome. Strong influences on cardiac repolarization occur during events encountered in everyday life and, when such influences are imposed on a diseased heart, they may contribute to stress-provoked arrhythmias.

References

1. Wasserburger RH, Siebecker KL, Lewis WC. The effect of hyperventilation on the normal adult electrocardiogram. Circulation 1956;13:850–5.

2. Bertolet BD, Boyette AF, Hofmann CA, Pepine CJ, Hill JA. Prevalence of pseudoischemic ST-segment changes during ambulatory electrocardiographic monitoring. Am J Cardiol 1992;70:818–20.
3. Sala S, Malfatto G, Locati EH, DeFerrari GM, Schwartz PJ. Diagnostic value of exercise-induced T wave abnormalities in the idiopathic long QT syndrome [abstract]. Circulation 1992;86 Suppl I:I-392.
4. Friesinger GC, Biern RD, Likar I, Mason RE. Exercise electrocardiography and vasoregulatory abnormalities. Am J Cardiol 1972;30:733–9.
5. Schwartz PJ, Malliani A. Electrical alternation of the T-wave: clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long Q-T syndrome. Am Heart J 1975;89:378–90.
6. Browne KF, Zipes DP, Heger JJ, Prystowsky EN. Influence of the autonomic nervous system on the QT interval in man. Am J Cardiol 1982;50:1099–103.
7. Ahnve S, Vallin H. Influence of heart rate and inhibition of autonomic tone on the QT interval. Circulation 1982;65:435–9.
8. Franz MR, Swerdlow CD, Liem LB, Schaefer J. Cycle length dependence of human action potential duration in vivo: effects of single extrastimuli, sudden sustained rate acceleration and deceleration, and different steady state frequencies. J Clin Invest 1988;82:972–9.
9. Lecocq B, Lecocq V, Jaillon P. Physiologic relation between cardiac cycle and QT duration in healthy volunteers. Am J Cardiol 1989;63:481–6.
10. Akhras F, Rickards AF. The relationship between QT interval and heart rate during physiological exercise and pacing. Jpn Heart J 1981;22:345–51.
11. Staniforth DH. The QT interval and cycle length: the influence of atropine, hyoscine, and exercise. Br J Clin Pharmacol 1983;16:615–21.
12. Zaza A, Malfatto G, Schwartz PJ. Sympathetic modulation of the relation between ventricular repolarization and cycle length. Circ Res 1991;68:1191–203.
13. Davidowski TA, Wolf S. The QT interval during reflex cardiac adaptation. Circulation 1984;69:22–5.
14. Coghlan JG, Madden B, Norell MN, Ilsley CDJ, Mitchell AG. Paradoxical early lengthening and subsequent linear shortening of the QT interval in response to exercise. Eur Heart J 1992;13:1325–8.
15. Mitsutake A, Takeshita A, Kuroiva A, Nakamura M. Usefulness of the Valsalva maneuver in management of the long QT syndrome. Circulation 1981;63:1029–35.
16. Fredlund B, Olsson SB. The QT interval—estimation, variability, and the effect of physical exercise [abstract]. Eur Heart J 1985;6 Suppl D:175.
17. Schwartz PJ. Idiopathic long QT syndrome: progress and questions. Am Heart J 1985;109:399–411.
18. Wellens HJJ, Vermeulen A, Durrer D. Ventricular fibrillation occurring on arousal from sleep by auditory stimuli. Circulation 1972;46:661–5.
19. Schwartz PJ, Zaza A, Locati E, Moss AJ. Stress and sudden death. The case of long QT syndrome. Circulation 1991;83 Suppl II:71–80.
20. Lepeschkin E, Surawicz B. The measurement of the Q-T interval of the electrocardiogram. Circulation 1952;6:378–88.
21. Deanfield JE, Riberio P, Oakley K, Krikler S, Selwyn AP. Analysis of ST-segment changes in normal subjects: implications for ambulatory monitoring in angina pectoris. Am J Cardiol 1984;54:1321–5.
22. Chatterjee K, Harris A, Davies G, Leatham A. Electrocardiographic changes subsequent to artificial ventricular depolarization. Br Heart J 1969;31:770–6.
23. Taggart P, Carruthers M, Somerville W. Electrocardiogram, plasma catecholamines and lipids, and their modification by oxprenolol when speaking before audience. Lancet 1973:341–6.
24. Taggart P, Sutton P, Lab M, Dean J, Harrison F. Interplay between adrenaline and interbeat interval on ventricular repolarization in intact heart in vivo. Cardiovasc Res 1990;24:884–95.
25. Arnold L, Page J, Attwell D, Cannell M, Eisner DA. The dependence on heart rate of the human ventricular action potential duration. Cardiovasc Res 1982;16:547–51.
26. Seed WA, Noble M, Oldershaw P, et al. Relation of human cardiac action potential duration to the interval between beats: implications for the validity of rate corrected QT interval (QTc). Br Heart J 1987;57:32–7.
27. Laks MM. Long QT interval syndrome: a new look at an old electrocardiographic measurement—the power of the computer. Circulation 1990;82:1539–41.
28. Abildskov J. Adrenergic effects on the QT interval of the electrocardiogram. Am Heart J 1976;92:210–6.
29. Cappato R, Alboni P, Pedroni P, Gilli G, Antonioli G. Sympathetic and vagal influences on rate-dependent changes in QT interval in healthy subjects. Am J Cardiol 1991;68:1188–93.
30. Lau CP, Ward DE. QT hysteresis: the effect of an abrupt change in pacing rate. In: Butrous GS, Schwartz PJ, editors. Clinical Aspects of Ventricular Repolarization. London: Farrand, 1989:175–81.
31. Merri M, Alberti M, Moss AJ. Dynamic analysis of ventricular repolarization duration from 24-hour Holter recordings. IEEE Transact Biomed Eng 1993;40:1219–25.
32. Viitasalo M, Karjalainen J. QT intervals at heart rates from 50 to 120 beats per minute during 24-hour electrocardiographic recording in 100 healthy men. Effects of atenolol. Circulation 1992;86:1439–42.
33. Lax KG, Okin PM, Kligfield P. Electrocardiographic repolarization measurements at rest and during exercise in normal subjects and in patients with coronary artery disease. Am Heart J 1994;128:271–80.
34. Kadish AH, Weisman HF, Veltri EP, Epstein AE, Slepian MJ, Levine JH. Paradoxical effects of exercise on the QT interval in patients with polymorphic ventricular tachycardia receiving type Ia antiarrhythmic agents. Circulation 1990;81:14–9.
35. Browne KF, Prystowsky E, Heger JJ, Chilson DA, Zipes DP. Prolongation of the QT interval in man during sleep. Am J Cardiol 1983;52:55–9.
36. Schwartz PJ, Priori SG, Locati EH, et al. QTc responses to mexiletine and to heart rate changes differentiate LQT1 from LQT3 but not from LQT2 patients [abstract]. Circulation 1996;94 Suppl I:I-204.
37. Schwartz PJ, Wolf S. QT interval prolongation as predictor of sudden death in patients with myocardial infarction. Circulation 1978;57:1074–7.
38. Ward DE. Prolongation of the QT interval as an indicator of risk of a cardiac event. Eur Heart J 1988;9 Suppl G:139–44.