Automatic measurement of corrected QT interval in Holter recordings: Comparison of its dynamic behavior in patients after myocardial infarction with and without life-threatening arrhythmias

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This study was designed to determine the value of automatic corrected QT-interval measurement in Holter tapes in patients after myocardial infarction as a marker of life-threatening ventricular arrhythmias. We compared the corrected QT interval, automatically measured in 24-hour Holter recordings, in two groups of patients after myocardial infarction: group I was composed of 14 patients admitted consecutively to our hospital for documented sustained ventricular tachycardia or out-of-hospital cardiac arrest. Group II consisted of 28 patients with previous myocardial infarction with characteristics similar to those of group I, but without malignant ventricular arrhythmias in the follow-up. The global mean 24-hour corrected QT interval was longer in group I (425 ± 20 msec) than in those patients after myocardial infarction without arrhythmias (group II) (405 ± 17 msec; $p < 0.01$). Furthermore, a significant proportion of patients of group I (seven of 14) exhibited more peaks of corrected QT longer than 500 msec compared with patients of group II (two of 28; $p < 0.005$). A circadian rhythm of corrected QT peaks was observed in group I, having a significantly higher incidence from 11 PM to 11 AM ($p < 0.05$). We conclude that automatic corrected QT-interval measurement on Holter electrocardiogram is now available and feasible. Our results suggest that this is a marker for risk assessment of life-threatening ventricular arrhythmias. Large-scale trials are needed to confirm these results and to determine the predictive value of this technique for risk stratification. (Am Heart J 1997;134:181-7.)

Ischemic heart disease is one of the most important causes of death in the adult population. Approximately 50% of deaths in these patients are sudden. It is necessary to stratify the risk of sudden death, particularly after myocardial infarction. Malignant ventricular arrhythmias, such as ventricular fibrillation or sustained ventricular tachycardia, are the most frequent arrhythmias involved in the process of sudden death. In patients after myocardial infarction, these arrhythmias usually appear when different trigger mechanisms act on a vulnerable myocardium.[1,2] The most important markers of myocardial vulnerability are depressed left ventricular function, size of infarction scar, residual ischemia, frequent and repetitive premature ventricular contractions, and autonomic nervous system disturbances.[3-6]

The QT interval, which represents the total duration of depolarization and repolarization of the myocardium, is an electrocardiographic parameter modulated by the autonomic nervous system. Because of the short duration of the QRS complex, changes in QT duration encompass changes in the repolarization process. In the last year interest was expressed in the prolongation of repolarization, and thus of the QT interval, and the incidence of malignant ventricular arrhythmias and sudden cardiac death.

Clinical interest in the lengthening of the QT interval as a marker of sudden death began with the description of the congenital long-QT syndrome.[7-9] In recent years, several studies[10-17] examined the relation between the QTc (QT interval corrected according to Bazett's formula) prolongation on surface electrocardiogram (ECG) and prognosis after acute myocardial infarction. Nevertheless, little information is available regarding the value of serial determinations and the

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Table I. Clinical characteristics of patients after myocardial infarction: Patients with and without life-threatening arrhythmias

	Group I (n = 14)	Group II (n = 28)	p Value
Sex (M/F)	12/2	25/3	NS
Age (yr)	59 ± 13	57 ± 10	NS
Anterior MI	9 (64%)	16 (57%)	NS
LV ejection fraction (%)	40 ± 6	44 ± 8	NS
LV ejection fraction <40%	6 (42%)	13 (46%)	NS
Angina	3 (21%)	7 (25%)	NS
Diabetes mellitus	3 (21%)	8 (28%)	NS
Hypertension	8 (57%)	15 (53%)	NS

MI, Myocardial infarction; *NS*, not significant.

dynamic behavior of the QTc interval in risk stratification after myocardial infarction.[18-21]

The aim of this study was to determine the value of automatic QTc measurement in Holter recordings in patients after myocardial infarction as a possible marker of life-threatening arrhythmias in the follow-up. The study used a new computer algorithm, which was previously described and validated.[22]

Patients and Methods

Patients

We studied two groups of patients by using a case/control design. Group I comprised 14 patients with prior myocardial infarction admitted consecutively to the coronary care unit with documented sustained ventricular tachycardia (eight patients) or out-of-hospital cardiac arrest (six patients). We included only patients whose arrhythmia appeared after the acute phase of myocardial infarction. The malignant ventricular arrhythmia appeared between the subacute phase and the second month (19 ± 5 days) after myocardial infarction in seven patients (two out-of-hospital cardiac arrests, five sustained ventricular tachycardias) and later (73 ± 58 months) in the remaining seven patients (four out-of-hospital cardiac arrests and three sustained ventricular tachycardias). None of these arrhythmias was related to clinical or ECG evidence of myocardial ischemia.

Group II was composed of 28 patients after myocardial infarction matched to group I for age, sex, clinical state, radionuclide left ventricular ejection fraction, and infarction location, but without malignant ventricular arrhythmias (Table I). Patients with bundle branch block, supraventricular arrhythmia, or an implanted pacemaker were excluded. Patients taking psychotropic or antiarrhythmic drugs or other cardioactive drugs known to influence QT duration and those with electrolytic disturbances also were excluded.

Continuous ECG recording

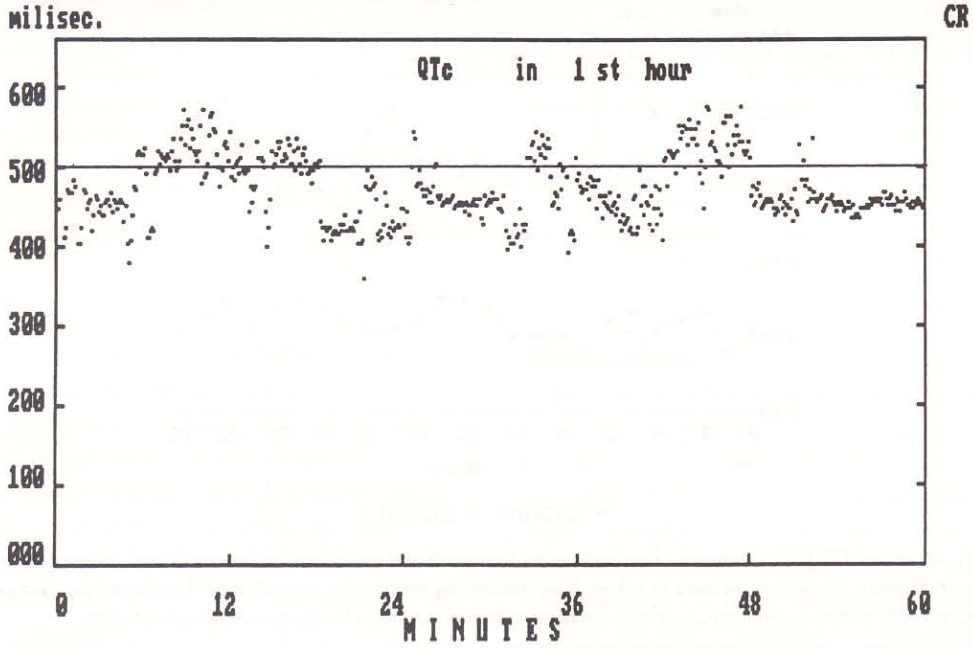
Twenty-four hour Holter monitoring recordings with a three-channel system were performed in both groups or before hospital discharge after myocardial infarction or as a routine screen in the follow-up. In group I the Holter recordings analyzed were performed ≤1 year before the arrhythmic event. At least 22 hours of recording were readable in each tape.

The bipolar electrodes were attached in the CM3 and CC5 positions. A Nihon Kohden DMC 3153K recorder with a frequency response from 0.05 Hz to 70 Hz (3 dB) was used, and the recording tapes were analyzed on a Nihon Kohden 3000K system. The channel with the best signal-to-noise ratio was selected for automatic QT analysis.

Algorithm for automatic QTc analysis

Analog ECG signals were digitized with a resolution of 12 bits by using a data-acquisition system installed on a Compaq 386/20 computer. Data were stored in the computer for subsequent detailed analysis. To measure the QTc interval, the onset of the QRS and the end of the T wave were detected by using an algorithm previously reported in detail.[22] It includes the following basic steps: ECG signal preprocessing with a low-pass differentiator, QRS detection and definition, T wave-end definition, and finally QT value selection. The T wave-end definition is based on the first derivative of the ECG signal. To identify T-wave end, a search window was defined from the QRS position. The highest slope value of the downward side of T wave (upward if the T wave is inverted) is the maximum (minimum in the inverted T wave) in the differentiated ECG signal in the previously defined window. A threshold is defined as this slope value divided by a constant factor. The T-wave end is marked when the differentiated signal reaches this threshold. Incorrect QT-measurement selection can result when noise, premature ventricular complexes, or other abnormalities are present. QT values that were >15% different from the current QT average were therefore rejected. The remaining beats were grouped into five measurement sets. In addition, beats whose QT value was the maximum or the minimum in each set were rejected as possible wrong data (noise or ectopic beats). Finally the QT interval was corrected by using Bazett's formula.[23] Data were recorded in a digitized form and represented graphically as a trend. In

Figure 1



Peaks of corrected QT (QTc)-interval lengthening >500 msec taken from 1 hour of Holter monitoring in one patient of group I. Each point was average measured QTc interval of 6-second periods.

Table II. Automatic corrected QT (QTc) interval analysis in two groups of patients after myocardial infarction

	Group I (n = 14)	Group II (n = 28)	p Value
Total of beats automatically analyzed	682,960	1,276,498	–
Mean QTc interval (msec)	425 ± 20	405 ± 17	<0.01
Mean QT interval (msec)	376 ± 33	373 ± 30	NS
Mean R-R interval (msec)	780 ± 80	830 ± 114	NS
Total number of peaks of QTc >500 msec	11,112 (1.62%)	823 (0.06%)	<0.005
Patients with peaks of QTc >500 msec	7 (50%)	2 (7%)	<0.005
Patients with grouped peaks (clusters) of QTc >500 msec	4 (28%)	None	<0.02

MI, Myocardial infarction; *NS*, not significant.

the trend, each point was the average measured QTc interval of 6-second periods. Thus each point represents a different number of beats, depending on the heart rate at that moment (Fig. 1).

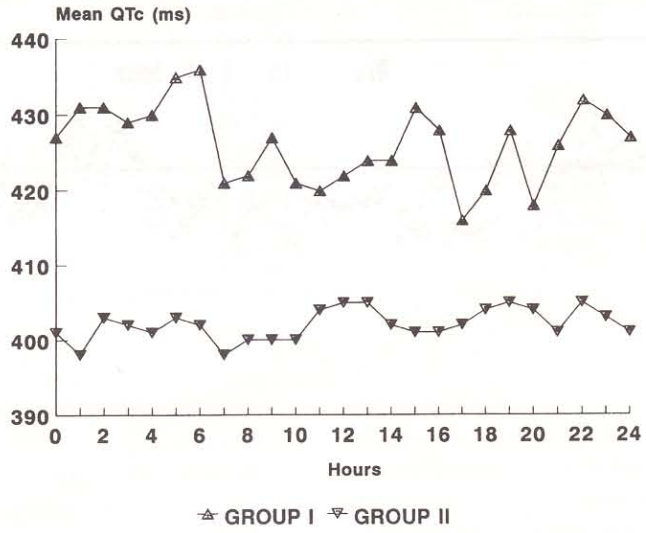
Validation of the algorithm

This algorithm was validated by manual determinations performed by two experts on ≥ 650 beats from 18 different Holter tapes chosen at random.[22] Manual measurements were done from the Holter ECG recordings printed at 25 mm/sec speed. To measure the QT manually, a tangent to the steepest portion of the downsloping or upsloping T wave was drawn, and the intersection of this tangent with the isoelectric line was defined as the T-wave end point. The mean errors between manual and automatic measurements were 2.4 ± 17.4 msec and 2.0 ± 14.0 msec, respectively. A mean error of 1.9 ± 10 msec was found between the manual measurements performed by two observers. QTc measurements performed automatically were thus comparable to manual measurements.[22] Although a small difference is present between the mean measurements of the whole QT values, standard deviation is high.

Definitions

Peaks of QTc lengthening were defined as the presence of intermittent QTc values longer than a determined cut-off point. We considered that clusters existed when the peaks were grouped and lasted at least 1 minute.

Figure 2



Plot of mean hourly corrected QT (QTc) interval of patients after myocardial infarction with (group I) and without (group II) life-threatening ventricular arrhythmias. Note that patients in whom life-threatening ventricular arrhythmias developed had longer QTc over 24-hour period compared with patients after myocardial infarction who did not have life-threatening arrhythmias.

Table III. Patients with peaks of corrected QT (QTc) lengthening according to a determined cut-off value

Peaks of QTc interval (msec)	Group I (n = 14)	Group II (n = 28)	p value
>440	14 (100%)	20 (71%)	NS
>460	10 (71%)	14 (50%)	NS
>480	7 (50%)	8 (28%)	NS
>500	7 (50%)	2 (7%)	<0.005

Statistics

To evaluate differences between groups I and II, we used the t test for continuous variables and the chi-square with the Yates correction for categoric variables. A p value <0.05 was considered statistically significant. Values are expressed as mean ± standard deviation. Logistic regression for matched groups was used to determine independent risk variables.

Results

Mean QTc and R-R interval

Beats (682,960 and 1,276,498) were automatically selected for QTc measurement from Holter tapes in groups I and II, respectively, according to the method described previously.[22] Mean QTc in 24-hour monitoring was longer in group I (425 ± 20 msec) than in group II (405 ± 17 msec; $p < 0.01$). The R-R interval was not significantly different between the groups (780 ± 80 msec vs 830 ± 114 msec, respectively), and no differences were present in the noncorrected mean QT interval in both groups (376 ± 33 msec vs 373 ± 30 msec; Table II). Fig. 2 shows the mean QTc intervals plotted against absolute time of day.

Circadian rhythm of mean QTc and R-R intervals

Although group I had a longer mean of QTc from 11 PM to 11 AM in comparison with from 11 AM to 11 PM (430 ± 18 msec vs 425 ± 19 msec), this did not reach statistical significance (Fig. 2). Also, the R-R interval was similar from 11 PM to 11 AM in comparison with that from 11 AM to 11 PM (792 ± 80 msec vs 785 ± 77 msec).

Peaks of QTc lengthening

At a cut-off point of the QTc value of 500 msec, significantly more patients were found in group I compared with group II: seven (50%) patients in group I who had peaks of QTc more than this value compared

Table IV. Circadian rhythm of peaks and clusters of corrected QT (QTc) lengthening >500 msec in patients after myocardial infarction with malignant ventricular arrhythmias (group I)

	24 hr of Holter	11 AM to 11 PM	11 PM to 11 AM	*p* Value
Number of peaks of QTc >500 msec/hr	463 ± 315	336 ± 176	590 ± 375	<0.05
Percentage of peaks of QTc >500 msec/hr	4.17 ± 2.83	3.02 ± 1.58	5.31 ± 3.37	<0.05
Number of grouped peaks (clusters) with QTc lengthening >500 msec/hr	1.29 ± 1.1.27	0.84 ± 0.83	1.75 ± 1.48	NS
Mean duration (min) of the grouped peaks (clusters) per hour	7.41 ± 8.31	2.85 ± 1.95	10.60 ± 9.64	<0.04

Results represent mean ± SD taken from hourly Holter monitoring within time indicated. The *p* values express differences between time from 11 AM to 11 PM vs that from 11 PM to 11 AM.

with two (7%) in group II ($p < 0.005$; Table III). At QTc values <500 msec, no statistical significance between both groups was reached (Table III). In addition, grouped peaks (clusters) of QTc lengthening >500 msec were found in four (28%) patients in group I and in none in group II ($p < 0.02$; Table II). The sensitivity of the presence of QT peaks is only 50%, but the specificity is very high at 93%. The presence of grouped peaks (clusters) has a lower sensitivity (28%), but the specificity is 100%. Positive and negative predictive values cannot be calculated with our cohort of patients because they are not a consecutive postinfarction population.

Furthermore, patients in group I had 11,112 beats (1.62%) with QTc >500 msec whereas those in group II only had 823 (0.06%; $p < 0.005$; Table II). The peaks of QTc >500 msec in group I were 463 ± 315 per hour throughout the 24 hours of Holter monitoring (Table IV). A trend of automatic QTc measurement showing clusters of QTc lengthening taken from 1 hour of Holter monitoring in one patient of group I is shown in Fig. 1. Univariate analysis shows that QTc peaks and mean QTc are different in both groups. However, logistic-regression analysis shows that only QTc peaks are an independent variable for malignant ventricular arrhythmias ($p < 0.005$).

Circadian rhythm of peaks. It was found that the number of peaks of QTc >500 msec and the percentage of peaks distributed per hour were greater from 11 PM to 11 AM than from 11 AM to 11 PM ($p < 0.05$; Table IV).

In the grouped peaks (clusters) >500 msec, although there were more from 11 PM to 11 AM in comparison with those from 11 AM to 11 PM, this did not reach statistical significance ($p = 0.07$). However, the mean duration of clusters (expressed in minutes) was longer in the former period than from 11 AM to 11 PM ($p < 0.04$; Table IV).

Discussion

The role of QTc lengthening as a marker of arrhythmic events in patients after myocardial infarction was first demonstrated in surface ECGs by Schwartz et al.[10] and others.[11-14] Nevertheless, some discordant results were published.[15-17] These conflicting results could be explained by different procedures for measuring QT interval or by QT variability resulting from circadian rhythm. Recently increasing importance is been given to the dynamic behavior of QT during exercise[18,19] or in Holter tapes.[20,21]

Our aim was to know whether changes in QT interval found in a Holter recording made at any time outside the acute phase of myocardial infarction may be used as a marker of arrhythmic events in the future. We did not study whether changes in QT act as a triggering mechanism in sudden death. To do this, we would have to study tapes of patients who died while wearing Holter devices.[24]

We previously reported the dynamic behavior of the QT interval of patients after myocardial infarction measured manually on Holter tapes.[21] The results were compared with a matched group of patients after myocardial infarction without malignant ventricular arrhythmias and with a control group. The mean value of the QTc interval of the two groups of these patients in this study was not statistically different. However, patients after myocardial infarction in whom malignant ventricular arrhythmias developed in the follow-up had peaks of QT >500 msec more frequently than did patients after myocardial infarction without malignant ventricular arrhythmias in the follow-up.

As manual measurement in Holter tapes is not feasible in clinical practice, it is clear that automatic measurement of the QT interval is necessary to comprehend fully the dynamic behavior of the QT interval over a 24-hour period. Several computerized systems measure the QT interval from single-lead recordings

made during ambulatory monitoring.[25,26] In this study we used an algorithm that we have previously described[22] for the automatic measurement of the QTc interval in Holter tapes. When we validated the measurement manually, an excellent correlation was obtained.[22] Although there are different formulas for correcting the QT interval for heart rate,[23,27-29] we used Bazett's formula because it is the most used in clinical practice and it fit this relation adequately.[29]

In our study, the global mean QTc was longer in the group of patients with malignant arrhythmias. This may be because a greater number of peaks >500 msec were present in this group. We also observed that a large proportion of patients after myocardial infarction with life-threatening ventricular arrhythmias had a greater number of QTc values in the form of peaks and clusters of peaks of QTc compared with the group without these arrhythmias. This finding could be related to the time (periods with peaks of QTc >500 msec) during which the patient would be at risk of sudden death. Our study concurs with that of Roden,[30] who suggested that the risk of malignant ventricular arrhythmias is greatly increased in the presence of a QTc interval >500 msec. There is recent evidence that the QTc interval varies from day to night in normal subjects. It has been demonstrated that sympathetic and parasympathetic tone alters the relation between QT interval and heart rate, and as a consequence, QTc varies with changes in the autonomic tone.[31] Recent data obtained from ambulatory Holter monitoring studies[31-33] demonstrated a high degree of spontaneous variability in the QTc, even over a single day and under stable conditions. Nevertheless, although >50% of normal patients (11 of 20) had a maximal QTc of >440 msec, only 1 had a maximal QTc of >500 msec (506 msec). Thus 500 msec may be considered a cut-off value to separate normal from abnormal QTc values in Holter tapes.[32,33] Furthermore we found a circadian rhythm with an increase in the number of peaks of QTc >500 msec from 11 PM to 11 AM. Although the number of peaks grouped as clusters was similar during the day and night, these lasted longer during the night because of a higher number of peaks in this period. Our results are in agreement with the circadian pattern of sudden cardiac death.[34-36]

Algra et al.[20] recently published a study in which the QTc interval on Holter tapes was measured automatically in a heterogeneous cohort of patients. They found that both prolonged mean QTc (>440 msec) and shortened mean QTc (<400 msec) derived from 24-hour ECGs were associated with a twofold risk of sudden death in comparison with intermediate QTc values (400 to 440 msec). These controversial results could result from the fact that, first, the study was performed by using a different design (only half of patients had a history of myocardial infarction, and a significant proportion of patients were taking drugs known to influence QT duration, which in turn could mislead QT analysis), and second, because an algorithm different from ours was used for automatic QT measurement.

Garson[37] showed that the QT interval measured on Holter tapes is discordant (longer or shorter) in comparison with that measured by using the same complexes on the standard ECG. The low-frequency response on the Holter ECG may be a limitation in producing a stable baseline[37] and cause a negative shift in the ST segment, negative overshooting of the offset of the T wave, or decreased amplitude of the T wave. It therefore seems advisable that studies of the dynamic behavior of QT by using Holter tapes should be compared with other Holter studies rather than with studies by using standard ECG.

We conclude that automatic QTc measurement from the Holter ECG is now available and feasible. The data from our study indicate that the global mean QTc value and the peaks of QTc >500 msec have been shown to be good markers for stratifying patients after myocardial infarction at risk of life-threatening arrhythmic events.

To confirm these results, a prospective large-scale trial in a cohort of patients after myocardial infarction is necessary, as this would show us the positive predictive value of these changes in QT interval. The automatically measured QTc interval could be added to other risk markers to increase predictive accuracy. Furthermore, because of the increasing importance given to the study of different values of QTc in different leads (QT dispersion),[38-40] it would be interesting to complement the dynamic behavior of QT interval in Holter tapes with the study of QT dispersion to enhance the performance of the QT interval in stratifying risk.

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