QT Dispersion: Comparison of Orthogonal, Quasi-orthogonal, and 12-Lead Configurations

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Background: Full standardization of QT dispersion has not yet been established; the influence of lead combination is still disputed. This study evaluates the respective value of automated $QT_{\rm c}$ dispersion in orthogonal (XYZ), quasi-orthogonal I-aVF-V2 (IF2), and 12-lead ECG configurations.

Methods: 15-lead digitized ECG recordings were collected in 92 normal subjects and in 71 patients following myocardial infarction. Each lead was processed by an automatic algorithm. QT dispersion was assessed by the range of individual QT intervals, both corrected by Bazett's formula. QT_c durations from all configurations were comparable (post-MI: 412 ± 27 vs 407 ± 29 msec for 12-lead and XYZ). Whatever the set of leads, QT_c interval was longer in post-MI (in 12-lead, 412 \pm 27 vs 397 ± 19 ms in normals, P < 0.001). QT_c dispersion was larger on 12-lead (post-MI: 51 ± 19 , 21 ± 13 and 28 ± 20 ms with 12-lead, XYZ and IF2); however, it was significantly larger in post-MI with all sets of leads (in XYZ 31 ± 13 vs 9 ± 7 ms in normal subjects 10 ± 0.0001 with all sets of leads (in XYZ, 21 \pm 13 vs 9 \pm 7 ms in normal subjects, P < 0.0001).

Conclusion: In conclusion, magnitude of QT dispersion depends on the set of leads considered; orthogonal configurations may still contain valuable prognostic information.

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QT interval; QT dispersion; 3-lead QT disperison; computerized electrocardiography

Disparity in myocardial repolarization time may result from inhomogeneity of regional action potential durations.1-6 Repolarization inhomogeneity has been observed within a wide variety of cardiac disorders, and it has been shown to constitute a substrate for malignant ventricular arrhythmias.5,7-17 in myocardial revascularization time may result from inhomogeneity of regional action potential durations.1-6 Monophasic action potentials recordings can be used to investigate repolarization dispersion. 1,3,6 Noninvasively, repolarization inhomogeneity was initially assessed by detailed body surface mapping involving more than 100 surface leads. 4,5,12 However, repolarization dispersion can be indirectly assessed as the difference in the QT interval durations measured on 12 surface ECG leads. 11,18 Despite the reduced number of explored sites, 12-lead QT dispersion is significantly correlated with dispersion of monophasic action potential durations,6 and it provides an important clinical tool in several myocardial diseases.7-20

A further reduction in the number of leads, either from the original set of 12 standard leads or from XYZ orthogonal configuration, has been recently proposed.21-22 The main reason relates to the lack of automatic methods and the consequent time-demanding, error-affected, and poorly reproducible manual measurements.23-26 Preliminary results suggest that a specific set of three leads (I, aVF, V2) may provide reliable discriminant and prognostic information in ischemic heart dis-

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ease,21,22 but the same studies did not address the role of XYZ ECG data that were not acquired.

Orthogonal XYZ configuration is now frequently available because it is routinely used for late potentials analysis from the high resolution body surface ECG.27 In addition, this orthogonal configuration allows a vectorcardiographic approach with direct evaluation of the effects of repolarization dispersion on the spatial T-wave loop mor-

phology.²⁸

The significance of different 3-lead configurations with respect to the 12-lead ECG has not been investigated. The main objective of this study was to analyze QT dispersion on three separate sets of leads with a fully automatic technique. Sets of leads considered were standard 12, I-aVF-V2 (extracted from the 12), and XYZ. The ability of each of these configurations to discriminate between healthy subjects and postmyocardial patients was evaluated.

METHODS

Study Population

Two groups of patients were studied. The first consisted of 92 healthy individuals with a mean age of 28 ± 8 years (range: 20 to 48 years, male/female sex ratio 0.9). All normal subjects had no history of cardiovascular disease and were screened for normal physical examination, blood pressure, resting 12-lead ECG, and echocardiography. In addition, a negative exercise test was required for all subjects > 40 years.

The second group included 71 patients enrolled 4 to 6 weeks after the occurrence of an acute myocardial infarction (MI). Only patients receiving beta-blocking therapy (atenolol, metoprolol) and no other cardiac medication were recruited. Infarction site was anterior in 24 patients and inferior in 47. This group was characterized by a strong male predominance (65 males) and mean age was 54 ± 12 years (range: 29 to 78 years). Thrombolytic therapy or artery desobstruction was successful in 52 patients (73%). Mean left ventricular ejection fraction assessed by angiography was 52% \pm 11% (28% to 78%).

Data Acquisition and Repolarization Variables

All subjects were recorded with a MAC15 electrocardiograph (Marquette Electronics Inc., Milwaukee, WI, USA), which simultaneously acquires 12 standard leads (6 precordial plus 6 limb leads) and 3 optional leads, which in the present study were the Frank XYZ leads. For each lead, the recorder stores a sequence of 10 seconds of ECG data and the median beat obtained during the sequence. All data was digitized at 250 Hz with a resolution of 5 µvolt and transferred to a PC for dispersion analysis.

A dedicated automatic algorithm previously described²⁹ performed the analysis of QRS-T complexes in the median templates from each individual lead. In brief, before performing quantitative ECG measurements, the input signal is filtered to remove noise artifacts and both first derivative and integral sequences of QRS-T are calculated. The position of onset and offset of both the QRS complex and the T wave then are detected by identifying major deflections of the filtered signal associated with zero-crossing of the first derivative. When detected, U waves are excluded. Since automated measurements cannot be 100% accurate (particularly in the determination of pathological QT intervals), the observer systematically edits the automatic measurements and, when needed, modifies (move, insert, delete) the position of the fiducial points (4 ms stepwise). For each lead with validated cursors, the QT interval was defined as the time interval between the QRS onset and Twave offset. To maximize reproducibility in this study we only used the delete option, i.e., we excluded the leads where the algorithm clearly made a mistake related to uncommon or flat T-wave patterns. In any circumstance, automatic fiducials were never overridden.

Three sets of leads were considered: the standard 12 leads (12-L, i.e., 6 limb and 6 precordial leads), the orthogonal XYZ, and the quasi-orthogonal I, aVF, V2 (IF2). For each of these configurations two variables were calculated: (1) repolarization duration assessed by the mean QT interval and (2) the range of all available QT intervals (maximum minus minimum QT). QT durations and QT range parameters were corrected according to Bazett's formula by using the mean RR interval of the recorded 10-second ECG data (QTc, QTc Range).

Lead Contribution to QT Dispersion

To evaluate the relative importance of each lead with respect to repolarization dispersion, a weighted score distribution was introduced. Alone,

the absolute position of a lead in the sequence of QT interval durations is meaningless as the number of measurable QT in an individual subject is not fixed. Thus, a weighted method must take into account the number of leads. For each subject, the n leads with a measurable QT interval (n ≤ 15) were sorted from the shortest to the longest QT interval, and the two extreme leads were given a score of 0 and 1, respectively. All remaining leads were assigned an intermediate score value that took into account the leads with the same QT duration. A lead in a given position may be assigned a different score depending on the value of n (for instance a lead in second position will be assigned

a score of 0.11 with n = 10 and 0.07 with n = 15). Figure 1 is an example of this method.

Within each population, the global median score value of each lead was calculated. For a given lead, a low global score indicates that the lead tends to provide shorter QT intervals (early in the 15-lead sequence). Conversely, a lead with a high score indicates a lead with a QT interval that is generally late in the sequence. The choice of the global median avoids the influence of individual score outliers for often missing leads. Finally, this approach has the advantage of merging the information of minimum and maximum QT interval values in a single representation.

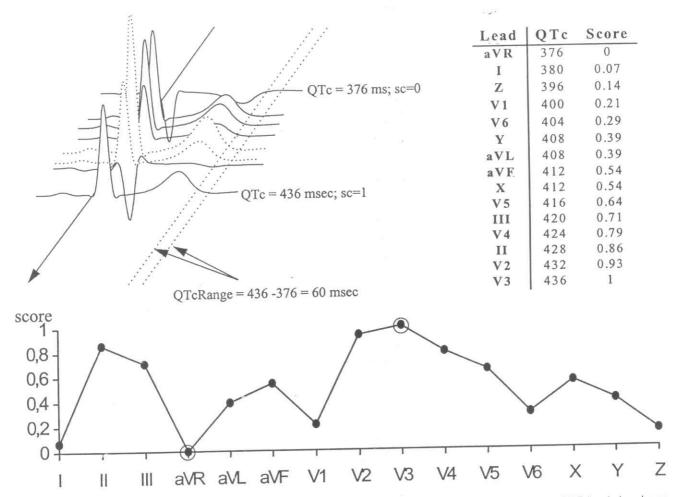


Figure 1. Upper left: The ECG leads are sorted according to increasing QT_c duration (only a subset of 15 leads has been depicted). In this example, QT_c Range is 60 ms. The two extreme leads (aVR shortest QT_c and V_3 longest QT_c) are given scores of 0 and 1, respectively. Upper right: Table displays all 15 leads with corresponding QT_c interval (ms) and score value. Leads with intermediate QT_c intervals are assigned intermediate score values. Leads with the same QT_c (e.g., V_6 and Y) are given the same score. In this specific example, all 15 leads have a measured QT_c . Lower: Graphic representation of score distribution. On horizontal axis, leads are organized from left to right as frontal, precordial, and orthogonal. Open circles identify the two extreme leads.

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Statistical Analysis

Data were expressed as mean \pm standard deviation. In each study population, the QT_c interval durations and dispersions obtained in the three sets of leads were compared by paired Student's *t*-test. Comparisons between controls and post-MI were performed using nonpaired Student's *t*-test, whereas global weighted scores were compared by analysis of variance for repeated measurements. A level of 0.05 was considered as significant.

Agreement between sets of leads on both QT_c duration and dispersion was assessed by the method described by Bland and Altman.³⁰ Briefly, if p and q are (within a subject) the respective measures from two sets of leads, p-q is the absolute error and (p+q)/2 is the average estimate. A plot of the absolute error against the average estimate displays the amount of agreement between the two measures. Numerically, the agreement is evaluated by calculating the mean (generally referred to as "bias") and the standard deviation of all absolute errors.²⁶ In addition, the mean of all relative errors (p-q)/[(p+q)/2] was calculated.

RESULTS OT Duration

12-Lead Data (Table 1)

RR interval, QRS duration, and QT_c duration were significantly larger in post-MI patients compared with controls. Within the normal group, females (n = 47) exhibited longer QT_c intervals than males (403 \pm 19 vs 392 \pm 17 ms, P = 0.008). The same result could not be confirmed in the post-MI population, probably due to the small number of females (n = 6). No differences were found in the

 QT_c durations between anterior and inferior MI (415 \pm 33 vs 411 \pm 25 ms).

Role of the Set of Leads on QT Duration

As shown in Table 2, mean QT_c intervals evaluated on different lead configurations are comparable with biases (mean absolute errors between two measures) ranging from 1 to 6 ms. Nevertheless, with paired *t*-test, statistical significance can be reached (in post-MI, 412 \pm 27 ms for 12-lead vs 407 \pm 29 ms for XYZ, P < 0.0001). Figure 2 shows a Bland-Altman plot for the bias between QT_c in 12-L and XYZ sets; the bias (5 \pm 10 ms) and relative error (1% \pm 2%) are small.

Whatever the set of leads, the two populations could be discriminated by QT_c interval (Table 1). Repolarization duration was consistently longer in post-MI patients (in 12-L, 412 \pm 27 ms vs 397 \pm 19 ms in normals, P < 0.001).

QT Dispersion

12-Lead data (Table 1)

 QT_c dispersion was larger after myocardial infarction (51 \pm 19 vs 34 \pm 11 ms, P < 0.0001). In controls, QT_c dispersion was significantly shorter in females (30 \pm 11 vs 38 \pm 10 ms in males, P < 0.001). Due to the sex ratio imbalance, no gender-related differences could be analyzed in post-MI patients. Repolarization dispersion was larger in anterior than in inferior MI (61 \pm 20 vs 45 \pm 15 ms, P < 0.001).

Role of the Set of Leads on QT Dispersion

Controls have a larger dispersion when 12-L lead configuration is used. This can be observed from Table 3 (QT_c dispersion: 34 ± 11 , 9 ± 7 , and $14 \pm$

Table 1. RR, QRS, QT_c and QT_c Range Values in Controls and in Post-MI Patients

	XYZ		12-L		IF2	
	Controls	Post-MI	Controls	Post MI	Controls	Post-MI
RR (ms)	_	_	884 ± 150†	1036 ± 166	_	
QRS (ms)			$90 \pm 9*$	94 ± 11	-	-
QT _c (ms)	$397 \pm 19†$	407 ± 29	398 ± 191	412 ± 27	$395 \pm 21 \dagger$	412 ± 25
QT _c Range (ms)	$9 \pm 7 =$	21 ± 13	$34 \pm 11 \pm$	51 ± 19	15 ± 9‡	28 ± 20

^{*} $P \le 0.01$.

 $t P \le 0.001$

 $P \le 0.0001$

Table 2. Comparison of QT_{c} Values Among the Lead Configurations Analyzed

QT _c (ms)	XYZ	XYZ vs 12-L	12-L	IF2 vs 12-L	IF2	IF2 vs XYZ
Controls	397 ± 19	1 ± 4 ms 0.3% ± 1%	398 ± 19	3 ± 11 ms 0.8% ± 3%	395 ± 21	2 ± 12 ms 0.5% ± 3% NS
Post-MI	407 ± 29	5 ± 10 ms 1% ± 2% ‡	412 ± 27	1 ± 10 ms 0.3% ± 2% NS	412 ± 25	6 ± 16 ms 2% ± 4% †

Bold numbers are QT_c intervals; values between QT_c intervals correspond to the biases (ms) and the relative errors (%) obtained with each comparison.

9 ms with 12-L, XYZ and IF2 configurations, respectively) and Bland-Altman plots (Figs. 3 and 4). Biases obtained were 25 ± 14 ms with a relative error of $114\% \pm 64\%$ (12-L vs XYZ) and 20 ± 12 ms with a relative error of $80\% \pm 47\%$ (12-L vs IF2). Comparison between QT_c dispersion from the two orthogonal sets of leads led to smaller bias and relative errors (6 \pm 12 ms and 47% \pm 102%, respectively).

The same kind of trends were observed in the post-MI population. Specifically, QT_c dispersion was significantly larger with 12-L (51 \pm 19, 21 \pm 13, and 28 \pm 20 ms with 12-L, XYZ, and IF2 configurations, respectively). In this population, biases obtained were 30 \pm 18 ms between 12-L and XYZ (relative error 82% \pm 49%) and 24 \pm 17 ms

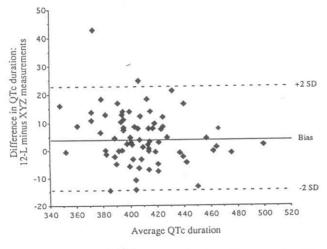


Figure 2. Bland-Altman plot for the differences in QT_c duration between 12-L and XYZ lead configurations in post-MI.

between 12-L and IF2 (relative error $60\% \pm 43\%$). As with controls, bias and relative errors obtained with comparison between QT_c dispersion from the two orthogonal sets of leads were smaller (7 \pm 18 ms and 28% \pm 71%).

Whatever the set of leads considered, QT_c dispersion was consistently larger after myocardial infarction (in XYZ, 21 ± 13 ms vs 9 ± 7 ms in normals, P < 0.0001).

Weighted Score Distribution

Figure 5 shows the median score value attained in control and post-MI groups for each lead. Anterior and inferior MI data are depicted separately. Median QT_c interval is consistently the longest in precordial lead V_3 (median score > 0.93). Lead II also provided a high score (close to V_3) but only in normals. Conversely, short QT score values were obtained in aVL and V_1 for the normals and in aVR for both post-MI subgroups. When considered in the sequence of 15 leads, XYZ provided intermediate score values. On the contrary, only two of the quasi-orthogonal leads (I and aVF) had intermediate scores, whereas the third (V_2) tended to be late in the sequence order of QT_c durations, particularly in post-MI subgroups.

Table III also outlines some aspects of QT_c lead distribution. Indeed, the smaller dispersion obtained from XYZ configuration is in accordance with the central position of these leads in the score distribution. In addition, XYZ average minimal and maximal QT_c durations are larger and smaller, respectively, than corresponding 12-lead intervals (in controls, minimal QT_c : 391 \pm 24 ms in XYZ vs 377 \pm 22 ms in 12-L; maximal QT_c : 402 \pm 19 ms in XYZ vs 411 \pm 20 ms in 12-L).

 $[*]P \le 0.01$.

 $tP \le 0.001$

 $P \le 0.0001$.

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Table 3. Role of Lead Configuration on QT Dispersion

				The Property Model Annual		
	XYZ	12-L vs XYZ	12-L	12-L vs IF2	IF2	IF2 vs XYZ
Controls		2.9		=		
Minimal QT _c	391 ± 24		377 ± 22		388 ± 19	
QT _c Range	9 ± 7	$25 \pm 14 \text{ ms}$	34 ± 11	$20 \pm 12 \text{ ms}$	14 ± 9	6 ± 12 ms
Maximal QT _c	402 ± 19	9 79 10	411 ± 20	20 = 12 1115	404 ± 19	0 = 12 1113
Post-MI		3.8.5				
Minimal QT	391 ± 27		382 ± 26		700 . 07	
					396 ± 27	
QT _c Range	21 ± 13	$30 \pm 18 \text{ms}$	51 ± 19	$24 \pm 17 \text{ ms}$	28 ± 20	$7 \pm 18 \text{ms}$
Maximal QT _c	416 ± 29	50	432 ± 29	32	427 ± 26	

Values between QT_c Ranges correspond to the biases obtained with each comparison.

Conversely, IF2 configuration provided closer to 12-L maximal QT $_c$ durations, particularly in post-MI patients (maximal QT $_c$: 416 \pm 29 ms in XYZ vs 427 \pm 26 ms in IF2 vs 432 \pm 29 in 12-L), thus explaining the larger QT $_c$ Range found with this set of leads.

DISCUSSION

This is the first study on QT_c dispersion that applied a fully automated technique for data acquisition and analysis. Then reproducibility is maximized. In addition, three simultaneously acquired sets of leads (standard 12 leads; orthogonal XYZ; and quasi-orthogonal I, avF, and V_2) were compared.

Two major findings are worthy of attention: (1) QT_c dispersion does change with lead configura-

tion, and 3-lead analysis shows a loss of information particularly striking in XYZ and (2) whatever set of lead is considered, QT_c dispersion is significantly larger in post-MI patients.

Methodology

Very few studies used 15 leads simultaneously acquired and digitized for repolarization analysis. ^{28,31} Then, problems related to paper printout speed, time shift between different subsets of leads does not concern this work. ^{23,26} More critically, determination of repolarization fiducial points was performed automatically, thus enhancing reproducibility of results. ²⁴ In the study by Zaidi et al. ³¹ only XYZ was performed automatically, but manual editing of fiducials on 12 standard leads was necessary. However, difficult T-wave shapes result

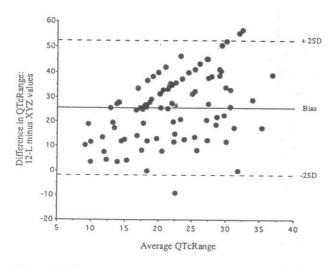


Figure 3. Bland-Altman plot for the differences in QT_c dispersion (QT_c Range) between 12-L and XYZ lead configurations in controls.

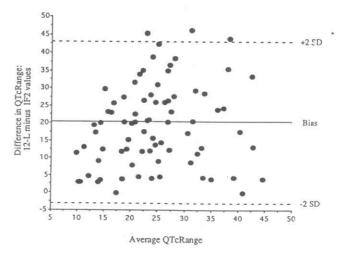


Figure 4. Bland-Altman plot for the differences in QT_c dispersion (QT_c Range) between 12-L and IF2 lead configurations in controls.

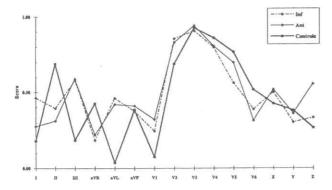


Figure 5. Global weighted score distributions in controls and post-MI patients (INF: inferior MI, ANT: anterior MI). The score value associated with each lead (horizontal axis organized as explained in Figure 1) represents the median value obtained in the respective population.

in inaccurate measurements of QT durations, specifically in post-MI. Since any operator intervention would affect (reduce) reproducibility, we deliberately chose to exclude only the leads where the algorithm clearly made a mistake. Our technique is original in this regard.

Many studies underlined the need of a reduced set of leads to cope with tedious and lengthy matters related to 12-lead QT dispersion.²¹ This kind of concern does not apply to our approach, for which the computer time used with 3 or 15 leads was essentially the same. Yet, in the forthcoming era of automatic ECG analysis, 3-lead configurations may remain the gold standard of ambulatory 24-hour ECG recording, and thus of potentially dynamic aspects of QT dispersion.

XYZ versus 12-Lead

In our study, 12-lead QT_c dispersion was compared in controls and post-MI patients with two different sets of 3 leads. Zareba²¹ and Glancy²² reported on the prognostic impact of QT dispersion measured from the quasi-orthogonal configuration (IF2) in patients with ischemic heart disease. However, in these studies, XYZ data were not acquired. Zaidi et al.³¹ did compare the role of lead combination on QT dispersion distribution. They also found that the magnitude of QT dispersion evaluated from a reduced lead combination is smaller than that observed with 12 leads. Although they did not use a fully automated technique, numerical values are close to those of this study; for instance in normals they reported an XYZ QT dispersion of

 11 ± 9 ms and in inferior MI 22 ± 19 ms. Of note, our population is well representative of current MI management, as a large number of subjects had been thrombolyzed and all were receiving betablockers.

The reduced magnitude of XYZ QT_c dispersion is easily grasped from the weighted score distribution. Indeed, all groups have intermediate XYZ score values and extremes are attained in standard and precordial leads. Furthermore, the difference in information provided by 12-lead and XYZ combination is outlined in the Bland-Altman plots (Figs. 3 and 4). The bias is actually in the range of XYZ QT_c dispersion and relative error is > 100%.

This could explain why, despite smaller values of QTc dispersion, the information contained in the XYZ lead can discriminate controls and post-MI patients. Zaidi et al.31 stated that the discriminant power of XYZ leads (in this case represented by the percentage of inferior and anterior MI patients whose QT_c dispersion values > 97.5 percentile value obtained from their normal population) was much greater than that of 12 lead. Thus, reduced magnitude of QT_c dispersion may not imply a lesser discriminant power. On the contrary, larger 12-lead QTc dispersion may be affected by nonphysiological components of ventricular repolarization dispersion, such as tangential orientation and projection of electrical vectors.31-33 Nevertheless, recent findings from our group showed that the presence of an electrophysiological substrate for repolarization inhomogeneity is associated with alterations in the morphology of spatial T-wave loop structure. In addition, these alterations are correlated with 12-lead QT dispersion.28 Thus, the larger 12-lead QT dispersion is not only a consequence of a larger number of projection axes, but is also related with a true pathophysiological mecha-

Role of IF2

This lead configuration had been introduced as an alternative to the true orthogonal XYZ combination, which is not always available in daily practice. As far as QT dispersion is concerned, the results of this study seem rather to indicate an intermediate role of the quasi-orthogonal combination. When compared to 12 lead, a bias of dispersion is still present, but with a smaller amplitude than that obtained with XYZ. This is probably due to the presence in this combination of the "extreme

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weighted score lead" V_2 , as shown in Figure 5. Not surprisingly, this combination can also discriminate the two populations. More generally, for a reduced lead combination to approach 12-lead QT dispersion, it should include the extreme leads displayed in Figure 5, i.e., II, V_2 , and V_3 for longer QT intervals, and I, aVL, and V_1 for shorter QT intervals. The closest 3-lead combination may depend on the population (kind of substrate) studied.

Limitations

The main limitation of this study is the relatively small number of post-MI patients investigated. This is the consequence of the recruitment criteria and, in particular, the treatment condition allowed for enrollment (beta-blocking therapy and no other cardiac medication). These enrollment criteria probably explain the unbalance between anterior and inferior infarction sites. However, the combination of a large percent of patients thrombolyzed (73%), and the systematic prescription of a beta-blocker makes our pathological population homogeneous and well representative of modern management of MI.

Another limitation is the lack of follow-up, which prevented evaluation of the prognostic value of QT dispersion when calculated from different lead configurations. This objective will have to be achieved on larger, well-balanced post-MI populations.

CONCLUSIONS

This study analyzes QT dispersion on three separate sets of leads with a fully automatic technique. QTc duration (assessed by the mean QTc interval of measurable leads) in normal subjects and post-MI patients shows minimal variations on different lead configurations. Conversely, QT_c dispersion does depend on the set of leads. A loss of information is particularly striking in XYZ leads, which contribute to intermediate QT interval durations with respect to extreme values given by complete 12-lead data. Accordingly, a scalar use of the three orthogonal leads cannot be considered a 12-lead surrogate. Nevertheless, QT_c dispersion calculated on any set of leads can discriminate controls from postinfarction patients. Therefore, despite a reduced magnitude of QT dispersion, orthogonal sets of leads may still contain valuable clinical information. It remains to be demonstrated whether these alternative lead configurations may provide a prognostic index of ventricular repolarization inhomogeneity.

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