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Computer-assisted Study of ECG Indices of the Dispersion of Ventricular Repolarization

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Abstract: A new computer-assisted method for the quantitative assessment of the dispersion of ventricular repolarization (DVR) has been developed. Through interactive editing of an averaged QRS-T cycle from a 15-lead electrocardiographic (ECG) record (12-lead ECG + XYZ leads), five ECG indices of DVR are automatically computed: they represent the maximal interlead difference of QT and the intervals from the J point to the T wave end, from the J point to the T wave apex, and from the T wave apex to the T wave end. The standard limits of these indices were then established in six clinical groups, including normal subjects and patients with left ventricular hypertrophy, with myocardial infarction, and with intraventricular conduction defect, all subjects being without ventricular arrhythmias and without interacting drugs. The mean values and percentile ranges of all DVR indices were lower in the normal group than in all pathologic groups. The 97.5th percentiles of the QT end dispersion and the JT end dispersion were, respectively, 65 and 76 ms in normal subjects, 84 and 86 ms in patients with inferior MI; 89 and 100 ms in those with anterior MI; 90 and 98 ms in those with left ventricular hypertrophy; and 94 and 99 ms in those with intraventricular conduction defects. This suggests that increased DVR is associated with the varieties of heart disease represented in this study, even in the absence of ventricular arrhythmias, and also that individual measurements of DVR used as predictors of future arrhythmic events should be referred to the standard range of their own clinical group. **Key words:** QT dispersion, heterogeneity of ventricular repolarization dispersion, computer analysis, ECG indices of dispersion.

Increased regional heterogeneity of ventricular repolarization is a marker of an arrhythmogenic substrate, and it has been associated with the occurrence of life-threatening ventricular arrhythmias (1–5). The inhomogeneity of the recovery process within the myocardium may be reflected on the surface electrocardiogram (ECG) as the interlead variability of the QT interval, hence the terms QT interval dispersion or QT dispersion (6,7). Recently, Zareba et al. have shown that not only QT interval dispersion per se but also other indices of repolarization inhomogeneity measured on the whole QRS-T complex can make an independent contribution to the prediction of arrhythmic cardiac death in patients with coronary artery disease (4).

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However, uncertainty remains with respect to the proper method of measuring QT dispersion from the ECG and with respect to the clinical value of other indices of ventricular repolarization inhomogeneity. Visual detection based on manual measurement is an inaccurate and time-consuming method, prone to intra- and interobserver variation and dependent on the technical quality of the tracings, on the heart rate, and on the morphology of the ST-T-U wave (8–10).

Techniques proposed for QT interval measurement include use of manually operated digitizing pads and a computerized method to automatically measure QT dispersion from hardcopy ECGs converted to digital records (11); however, these approaches are also rather cumbersome. Since digital records are readily available from most current ECG machines, we decided to develop a new computerized system for the quantitative assessment of the dispersion of ventricular repolarization (DVR) directly from digitized ECGs. Once a valid, easy-to-use method without the limitation of hand-made measurements has been set up, it becomes feasible to study the DVR in large groups of subjects in various clinical categories.

So far, only a limited amount of data has been published about the magnitude of the DVR and its prevalence in various categories of patients with different clinical conditions (7). The purpose of our study was twofold: (1) to design a new computerized method for the quantitative assessment of the DVR; and (2) to study the distribution of several ECG indices of dispersion in various clinical groups to establish "standard" limits in several categories of patients free from ventricular arrhythmias.

Materials and Methods

Study Population

The study population consisted of a subset of a large documented database, containing more than 4,500 digitized records of 15 simultaneously recorded leads (ie, a 12-lead ECG plus Frank orthogonal XYZ leads) from our hospital population. We selected 1,442 records subdivided into six clinical groups (Table 1): 1,000 normal subjects without organic heart disease; 100 patients with left ventricular hypertrophy; 100 patients with inferior myocardial infarction (MI); 100 patients with anterior MI; 100 patients with mixed (both anterior and inferior) MI; 30 patients with major intraventricular conduction defects (ie, QRS duration > 120 ms); and 12 patients with dilated cardiomyopathy. The group of subjects with no structural cardiac abnormality was composed of normal controls selected on the basis of history, physical examination, chest radiography, and in some cases, echocardiography. Most were ambulatory outpatients referred for systematic health checkup or hospitalized patients undergoing prospective workup before gynecologic or orthopaedic surgery. The diagnoses of ventricular hypertrophy, MI, and cardiomyopathy were all clinically validated on the basis of non-ECG information from various sources, such as history, physical examination, echocardiography, radionuclide scintigraphy, cardiac catheterization, and coronary angiography (12). The ECGs of most infarction patients were recorded after the acute phase, either in the cardiac ward or later during a subsequent hospital stay. Since the purpose of this study was to examine the distribution of various ECG indices of DVR in order to establish their standard limits, we excluded patients with a documented history of serious ventricular arrhythmias (eg, nonsustained or sustained ventricular tachycardia, ventricular fibrillation, and arrhythmic sudden death). We also excluded patients taking drugs that can affect the QT duration and dispersion at rest, such as digitalis, sotalol, amiodarone, and other class III antiarrhythmic drugs, as well as class IA and IC antiarrhythmic drugs and bepridil.

Table 1. Clinical Characteristics of the Study Population

Clinical Group	No. of Patients	Mean Age ± SD (years)	Sex (M/F)
Normal	1,000	46 ± 16	410/590
Left ventricular hypertrophy	100	64 ± 11	53/47
Inferior MI	100	58 ± 10	85/15
Anterior MI	100	56 ± 12	80/20
Mixed MI	100	61 ± 12	85/15
IVCD	30	61 ± 9	17/13
Dilated cardiomyopathy	12	46 ± 14	9/3

MI, myocardial infarction; IVCD, intraventricular conduction defects.

Computer Analysis: Automatic Wave Identification

To simultaneously record the 12 standard ECG leads and the 3 orthogonal Frank XYZ leads, MAC-15 ECG carts (Marquette Electronics, Milwaukee, WI) were used. Each record consists of 10 seconds of synchronously digitized 15-lead data sampled at 500 Hz, with a resolution of 5 μV for the least significant bit. The digital records are transferred to

floppy disks for further processing by an HP 9000/800 series minicomputer (Palo Alto, CA) and mass storage on optical disks. A special-purpose program proceeds to signal conditioning with square spline interpolation for baseline drift removal and to beat detection, classification, and selective beat averaging (Fig. 1). After normalization of the original data values (1 μV = 1 least significant bit or 1 mV = 1,000), the individual QRS complexes are located by analysis of the pseudospatial velocity curves obtained from the XYZ raw data ($\Delta X^2 + \Delta Y^2 + \Delta Z^2$). The onset of each individual sinus beat is taken as the reference point for the alignment of all consecutive beats incorporated into the averaging procedure. The averaging of the sinus beats is then performed without any other filtering technique. The fiducial points are identified on the resulting averaged P-QRS-T complex according to the recommendations for measurements standards in quantitative electrocardiography established by the European Common Standards for Quantitative Electrocardiography (CSE) working party (13). First, a template-matching algorithm is applied to the pseudospatial velocity curve of the averaged beat [abs (ΔX) + abs(ΔY) + abs(ΔZ)] to find the QRS onset (Q) and offset (J) and the end of the T wave (Te). At the point determined by the templates for the Q, J, and Te points, a correction can be made by considering the velocity at these points according to preset threshold values. Further adjustment of the J point can be made by means of a tangential fit to the end of the QRS complex; for the Te point, no correction is applied. In case no T wave is found, a theoretical Te is computed by means of the formula proposed by Rautaharju et al. (14). The averaged beats on all 15 leads are then realigned as referred to their isoelectric level, which is taken as the average of five to eight sample points preceding the QRS onset. The apex of the T wave (Ta) is identified by searching the maximum positive or negative amplitude, which must be larger than 80 μV in a search region extending from 40 ms after the J point up to Te in each of the 15 individual leads. In case of a biphasic T wave, the second peak, which is the more distant to the J point, is taken as the apex of the T wave. Extensive clinical validation of this automatic wave identification has been undertaken in our laboratory.

Computer-assisted Editing and Quantitation of Repolarization

The Q, J, and Te fiducial points, initially identified on the record of the three orthogonal XYZ leads, are fitted to the entire 15-lead record. A visual correction of these global limits is possible through an interactive color display terminal (emulation of terminal HP 2627A on a personal computer; scale factor for the Y axis, 1 mV = 5.4 cm and for the X axis, 100 ms = 22 mm [1 pixel = 2 ms]). By moving a cursor on the computer screen, the operator can modify the exact location of these global limits, which are thereafter retransferred to the 15-lead record. The operator can then verify and edit the location of the J and Te points on each individual lead across the 15-lead record, following the CSE recommendations for measurement standards (13). The J point is defined as the return of

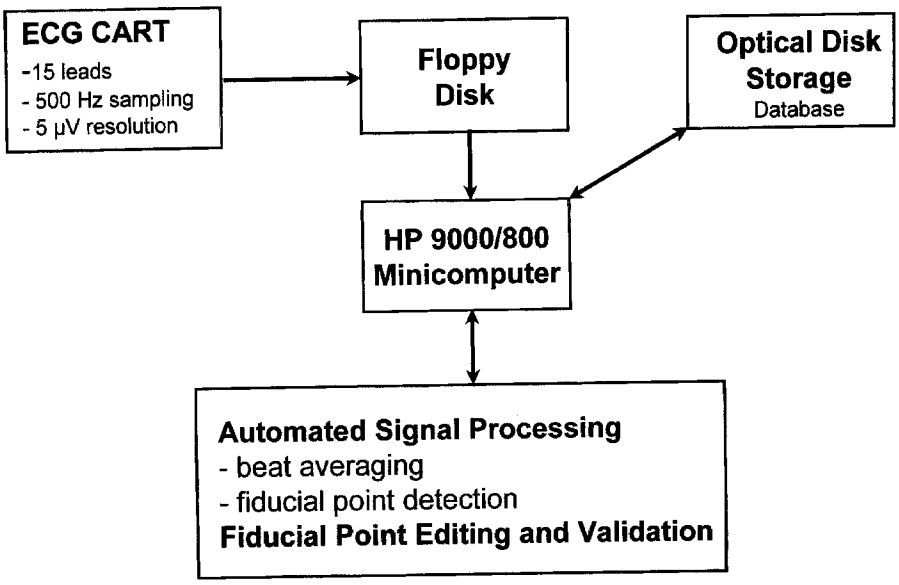

Fig. 1. Algorithmic flow chart for semiautomated analysis of ventricular repolarization.

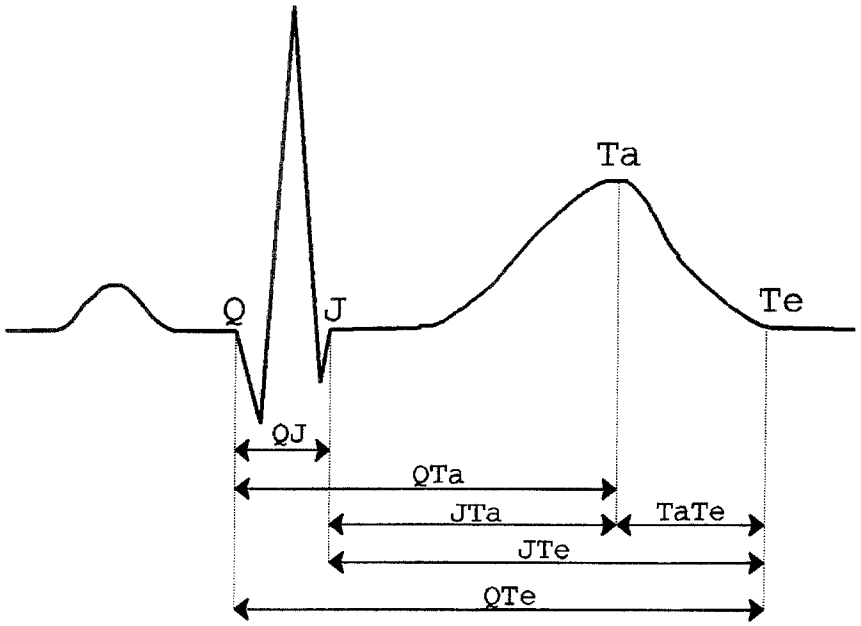

Fig. 2. After the validation of the fiducial points on the resulting averaged P-QRS-T complex, six intervals are automatically computed: QTe from QRS onset (Q) to T wave end (Te), QTa from QRS onset to T wave apex (Ta), JTe from J point to T wave end, JTa from J point to T wave apex, Ta-Te from T wave apex to T wave end, and QJ from Q wave onset to J point.

the QRS deflection to the isoelectric baseline or as the end of the velocity curve in the terminal part of the QRS deflection. The Te point is defined as the return of the distal limb of the T wave, after the T apex, to the baseline level. When a U wave is present, the QT and JT intervals are measured from QRS onset and offset, respectively, to the nadir of the curve joining the T and U waves. For this editing procedure, the data are presented on successive screen displays of (1) the orthogonal XYZ leads; (2) the six peripheral leads (I, II, III, aVR, aVL, aVF); and (3) the six precordial leads (V_1–V_6). In some cases, the operator can decide to reject a particular lead—for example, when determining the exact location of J or Te is impossible because of the absence of a clear return to the baseline level, because of the absence of a baseline velocity crossing, or because of a noisy lead. Exceptionally, the location of Te in a particular lead exceeds the global Te; in this case, that individual Te will be taken as a new global Te point. The entire procedure, including the automated processing and manual editing, requires about 3 minutes per case.

After the editing, several intervals are automatically computed (Fig. 2): QTe from QRS onset to T wave end, QTa from QRS onset to apex of T wave, JTe from J point to T wave end, JTa from J point to T wave apex, and Ta-Te from T wave apex to T wave end. All values are corrected according to heart rate by means of Bazett's formula (15). For each of these intervals, the difference between the maximal and minimal values across the 15 leads is taken as a potential index of DVR. Thus, five dispersion indices are available: the QTe dispersion (QTe-d), the QTa dispersion (QTa-d), the JTe dispersion (JTe-d), the JTa dispersion (JTa-d), and the Ta to Te dispersion (TaTe-d). The measure of the dispersion of ventricular depolarization (ie, QJ-d) was also assessed.

Statistical Analysis

A particular record was excluded from statistical analyses if it contained more than five leads rejected because of no reliable Te location, (ie, flat T wave) excessive noise level, or artifact. The data are presented as mean values ± 1 SD of all five ECG indices in every clinical group. One-way analysis of variance and Bonferroni's correction for multiple comparisons were used to test the differences in the dispersion indices between the clinical groups. Because of the small size of the cardiomyopathy group, no statistical conclusion could be drawn from that group.

Results

Table 2 shows the distribution of the six dispersion variables among the seven clinical groups. The mean values, standard deviations, and the 2.5th to 97.5th percentile ranges were smaller in the normal group than in the six pathologic groups for all variables except the duration of the QRS complex (QJ-d). Both QTe-d and JTe-d values were significantly smaller in the normal group than in all other pathologic groups ($P < .001$). Within the pathologic groups, the QTe-d values were lower in inferior MI

Table 2. Distribution of Index Values (ms) for Dispersion of Ventricular Repolarization Among Clinical Groups Indices

Group	QTe Dispersion	JTe Dispersion	QTa Dispersion	JTa Dispersion	TaTe Dispersion	QJ Dispersion
Normal (n = 1,000)	30.1 ± 15.1 9.0 → 65.3	36.8 ± 16.7 11.1 → 75.8	41.5 ± 18.4 11.9 → 82.7	48.8 ± 19.2 19.0 → 91.1	47.0 ± 17.0 20.3 → 84.8	14.5 ± 6.2 0.0 → 27.0
Left ventricular hypertrophy (n = 100)	42.8 ± 21.1 11.1 → 90.0	46.8 ± 21.7 15.5 → 98.0	59.4 ± 26.0 13.0 → 125.8	63.8 ± 25.1 24.0 → 132.0	59.6 ± 25.0 24.0 → 118.0	9.1 ± 5.7 0.0 → 19.0
Anterior MI (n = 100)	51.1 ± 19.7 13.9 → 89.5	6.6 ± 20.6 21.4 → 99.8	60.3 ± 25.8 8.7 → 95.4	65.8 ± 21.7 13.0 → 102.0	53.8 ± 25.6 20.4 → 100.0	17.6 ± 9.3 0.0 → 37.0
Inferior MI (n = 100)	40.1 ± 20.3 11.5 → 84.5	45.9 ± 20.1 18.5 → 86.0	43.2 ± 21.3 8.7 → 92.6	48.7 ± 20.1 12.4 → 90.0	46.7 ± 17.0 19.8 → 92.0	14.0 ± 5.9 0.0 → 27.0
Mixed MI (n = 100)	47.1 ± 20.9 14.3 → 86.7	52.4 ± 22.0 19.0 → 93.5	9.4 ± 28.1 11.7 → 122.8	64.3 ± 28.3 15.0 → 123.3	52.8 ± 23.5 20.7 → 125.0	13.7 ± 8.5 0.0 → 29.0
IVCD (n = 30)	59.6 ± 19.4 25.4 → 93.7	65.7 ± 21.2 30.1 → 99.1	69.8 ± 25.4 16.5 → 114.0	76.1 ± 23.9 28.2 → 122.0	67.7 ± 23.2 35.2 → 130.0	13.3 ± 9.5 0.0 → 27.5
Dilated cardiomyopathy (n = 12)	40.0 ± 19.3 13.8 → 77.0	45.5 ± 20.4 14.0 → 84.0	48.5 ± 41.0 0.0 → 135.0	52.9 ± 40.5 0.0 → 137.5	50.1 ± 39.3 0.0 → 117.0	9.2 ± 9.2 0.0 → 23.5

MI, myocardial infarction; IVCD, intraventricular conduction defects. Values are mean ± SD, range for 2.5th to 97.5th percentile.

than in anterior MI, and in intraventricular conduction defects, the values for inferior MI were closer to the normal values ($P < .001$). For JTe-d, there were only two significant differences: patients with left ventricular hypertrophy and those with inferior MI had smaller values than those with intraventricular conduction defects ($P < .001$). The QTa and JTa dispersion indices also exhibited lower values in the normal group than in all other groups except inferior MI ($P < .001$). Within the pathologic groups, inferior MI showed the smallest dispersion values. The TaTe dispersion indices were less discriminant, since in the normal group, values were significantly smaller than in the left ventricular hypertrophy and intraventricular conduction defect groups ($P < .001$) without significant differences as compared with other groups; neither was there a difference among the pathologic groups. The dispersion of QRS duration (QJ-d), which represents the variability of the J point as referred to QRS onset, was smaller in the left ventricular hypertrophy group then in the normal and all other pathologic groups except the intraventricular conduction defect group, thereby indicating a better stability of the J point identification in left ventricular hypertrophy patients.

Figure 3 shows the histograms of QTe dispersion in normal patients and in patients with inferior and anterior MI. The QTe dispersion indicates the amount of interlead dispersion of the whole electrical cycle, encompassing both depolarization and repolarization. The mean values were closer to each other in the normal (30 ± 15.1 ms) and in the inferior MI (40.1 ± 20.3 ms) groups, while the mean of the anterior MI group displayed a significantly higher value (51.1 ± 19.7 ms). However, the inferior MI group showed a somewhat bimodal distribution, with skewing to the right. If the 97.5th percentile was taken as the upper standard limit of QTe dispersion, the cutoff point would be 65.3 ms in normal subjects but 84.5 ms in patients with inferior MI and 89.5 ms in patients with anterior MI.

In Figure 4, showing the histograms of JTe dispersion in the same clinical groups, JTe-d indicates the amount of dispersion of the repolarization process only, thus excluding the depolarization represented by the QRS duration. For this index too, both the mean values and upper percentiles were shifted to the right in the anterior MI group as compared with the normal and inferior MI groups. Here, it was the anterior MI group that exhibited a somewhat bimodal distribution, with two peaks around 45 ms and 65 ms. The mean was 36.8 ms for normal subjects and 45.9 ms for the inferior MI group, versus 52.4 ms for the anterior MI group, and the 97.5th percentile was 75.8 ms for normal subjects and 86.0 ms for the inferior MI group, versus 99.8 ms for the anterior MI group.

Figure 5 shows the histograms for the distribution of the TaTe dispersion index, which belong to the late part of ventricular repolarization. There were no significant differences among the mean values of the three groups (Table 2). The rightward shift of the upper percentile of the MI groups as compared with the normal group was less pro-

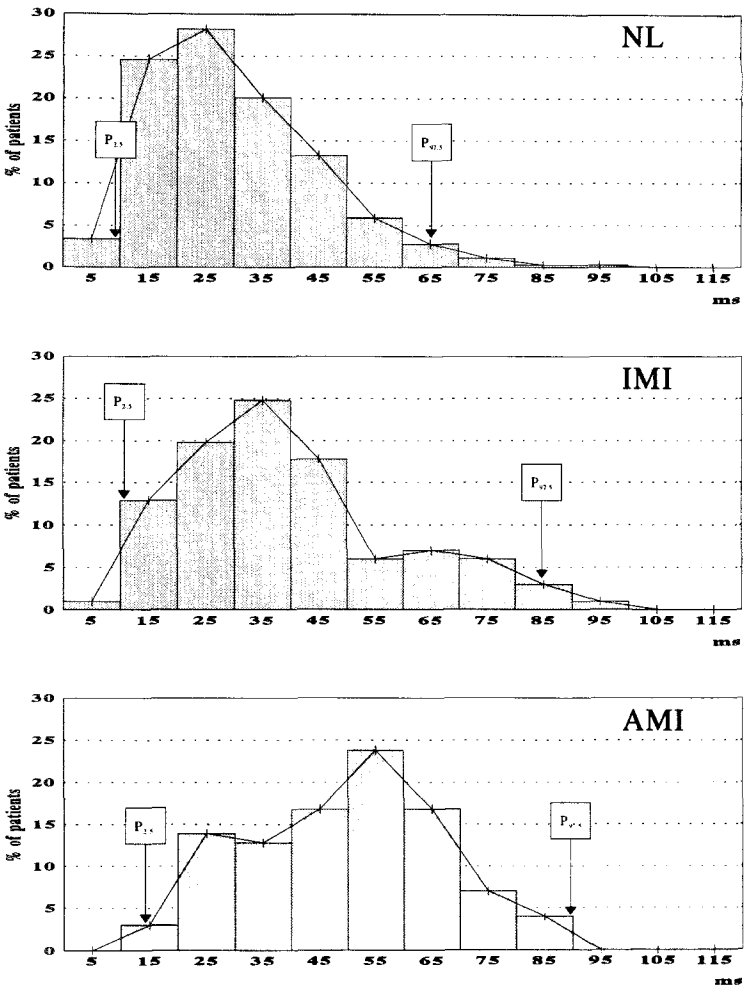

Fig. 3. Histograms of QTe dispersion index, highlighting the differences among three clinical groups: normal subjects (NL), and patients with inferior (IMI) and anterior (AMI) myocardial infarction. P2.5 and P97.5, 2.5th and 97.5th percentiles, respectively.

nounced than for the other ECG indices of dispersion representing the entire repolarization process (QTe and JTe) or its early part (QTa and JTa). Thus, we could not confirm that the TaTe interval is a more important segment of the ventricular complex harboring the DVR.

Figure 6 shows the relationship between the DVR and two anthropometric variables (ie, age and sex) in normal subjects. We found no correlation between age and DVR in the range 20–80 years. In healthy subjects of the same age, quite different values, ranging from 10 to 65 ms, can be observed. In the pathologic groups there also was no influence of patient age on dispersion values. As shown in Figure 6, the dispersion values were not significantly different between men and women. Thus, in this large population of 1,000 normal subjects, age and sex did not seem to influence the DVR.

Table 3 shows the dispersion values of QTe in three groups—normal, inferior MI, and anterior MI—according to various lead combinations. The values (mean ± SD and 97.5th percentile) were quite similar whether the 12 leads or the 15 leads were considered. Also, the discriminant power, which can be represented by the percentage of patients in the MI groups who had dispersion values exceeding the 97.5th percentile of the normal group, was only slightly higher with the 15-lead recording than with the 12-lead recording (15 vs 10% in inferior MI, 19 vs 16% in anterior MI), suggesting that there are probably no clinically significant differences between the two types of recordings. However, when only the three orthogonal XYZ leads were analyzed, the mean values of dispersion were much smaller in all three groups and the discriminant power was much greater, since 22% of the inferior MI patients and 46% of the anterior MI patients had values exceeding the 97.5th percentile of the normal group. Also shown in Table 3 are the results of dispersion values in various subsets of the 12 conventional leads. The discriminant power contained in the precordial lead or in the standard lead recordings was smaller than that of the 12-, 15-, or XYZ-lead recordings. There was a relationship between the location of infarction and the distribution of leads with larger

dispersion values and higher discriminant power. In inferior MI patients, the inferior leads II, III, and aVF exhibited the highest mean dispersion with a large standard deviation, whereas in anterior MI patients, these characteristics belonged to the precordial leads V_1 to V_4.

Discussion

Electrophysiology and ECG Indices of Dispersion of Repolarization

The DVR measured from the surface ECG is defined as the interlead variability in the duration of various intervals taken on the QRS-ST-T complex. So far, the most popular index of DVR has been the interlead QT variability described by Campbell et al. (16). In recent years, several studies have suggested that the DVR, far from being a technical artifact, may reflect spatial inhomogeneities in the recovery of ventricular excitability within the myocardium (3,6,17,18). In turn, this inhomogeneity or nonuniformity of ventricular recovery periods may form the electrophysiologic substrate leading to the occurrence of reentry and afterdepolarization mechanisms, which expose the patient to the risk of potentially lethal ventricular arrhythmias (1,19–22). Therefore, the DVR has been proposed as a useful, noninvasive marker of susceptibility to ventricular arrhythmias in a variety of cardiac conditions (5,23).

Among various ECG indices expressing the DVR, the QTe dispersion has thus far been the most widely studied. Several authors have shown a good correlation between changes in the DVR, as measured by epicardial monophasic action potential

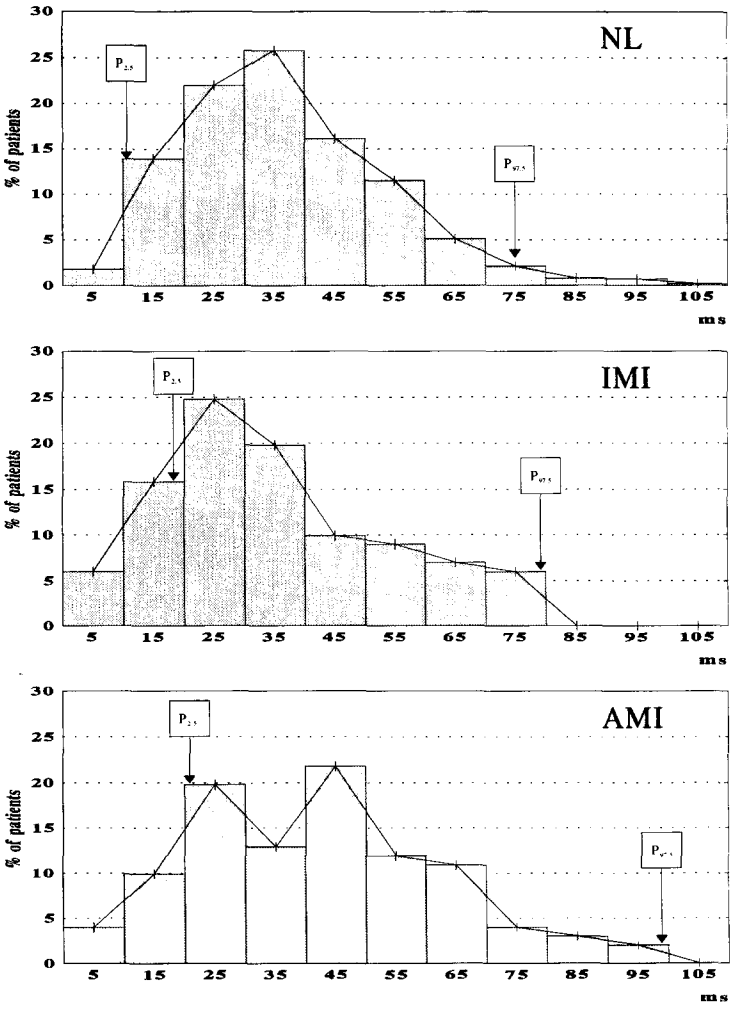

Fig. 4. Histograms of the JTe dispersion in normal subjects (NL) and patients with inferior (IMI) and anterior (AMI) myocardial infarction.

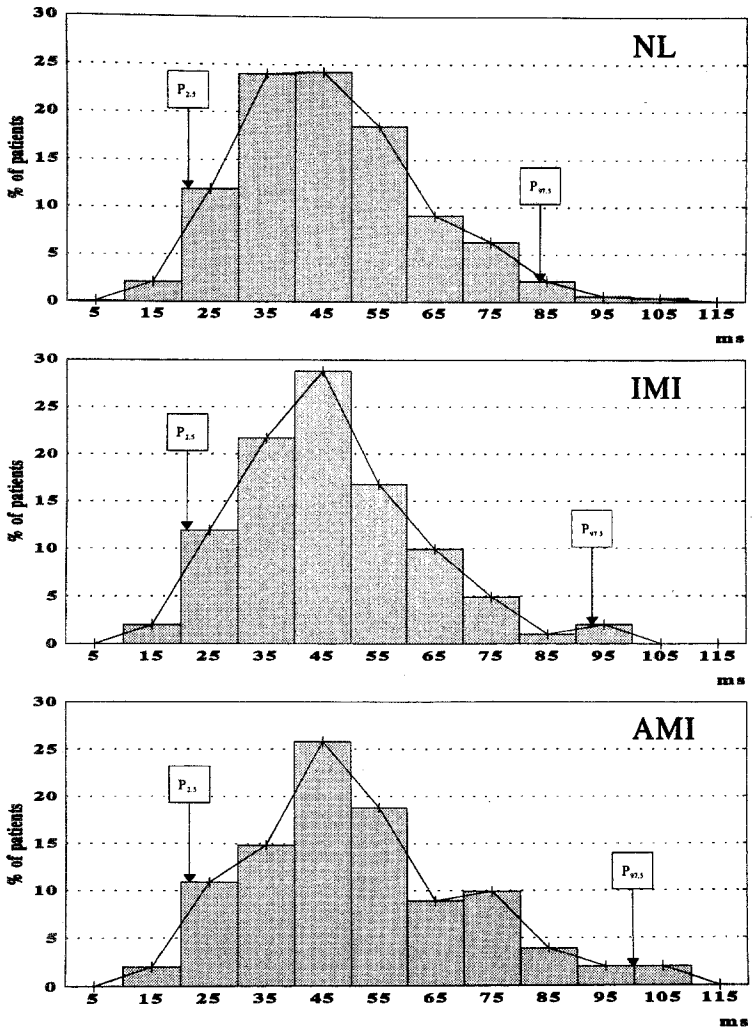

Fig. 5. Histograms of the Ta-Te dispersion, analyzing the last segment of the ventricular repolarization in normal subjects (NL) and patients with inferior (IMI) and anterior (AMI) myocardial infarction.

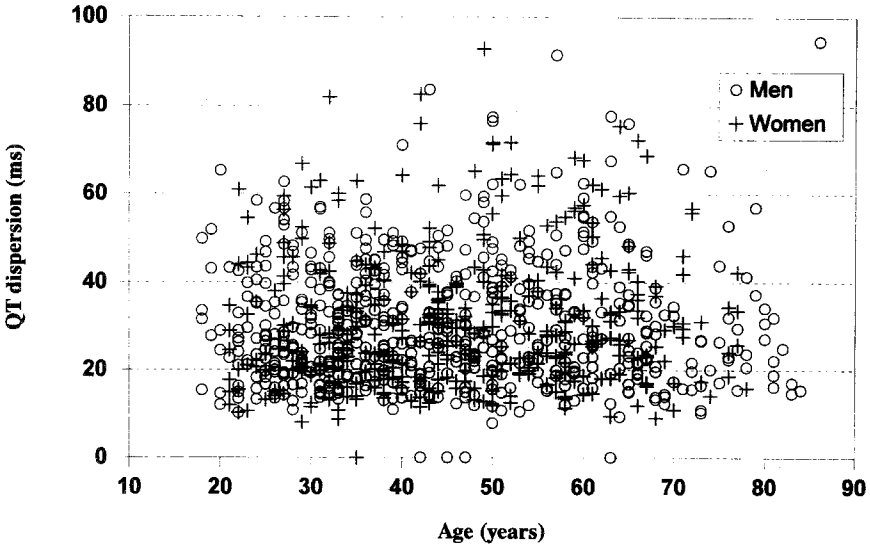

Fig. 6. There is no correlation between the age or sex and the dispersion of ventricular repolarization in normal subjects.

Table 3. Lead-dependent Distribution of QTe Dispersion Index and Percentage of Inferior MI and Anterior MI Patients Whose QTe Dispersion Values Exceed the 97.5th Percentile Values for Normal Subjects

	Normal (n = 1,000)		Inferior MI (n = 100)		Anterior MI (n = 100)	
QTe Dispersion	Mean ± SD (ms)	P97.5 (ms)	Mean ± SD (ms)	>P97.5 (%)	Mean ± SD (ms)	>P97.5 (%)
15 leads	30 ± 15	65	40 ± 20	15	51 ± 20	19
12 leads	29 ± 16	65	35 ± 19	10	47 ± 20	16
XYZ leads	11 ± 9	33	22 ± 19	22	29 ± 22	46
V_1–V_4 leads	16 ± 17	60	16 ± 17	5	26 ± 20	6
II, III, and aVF leads	9 ± 10	34	17 ± 15	1	13 ± 12	7
Precordial leads	18 ± 16	60	23 ± 20	9	37 ± 22	12
Standard leads	22 ± 15	57	24 ± 14	2	26 ± 16	7

MI, myocardial infarction; P97.5, 97.5th percentile.

recordings, and changes in the QT interval dispersion as measured from the surface ECG both in animal (24) and human models (25–27). However, other ST-T measurements may be valuable potential candidates for expressing DVR, and include the QTa, JTe, JTa, and Ta-Te dispersions, various measures of T wave area, rise time, and symmetry (4,24).

Methodology for Assessing Dispersion of Repolarization

In this study, we describe a new computer-assisted method for the quantitation of the DVR. This method has been applied to the normalization of various ECG indices of dispersion measured from 15-lead recordings. The usefulness of our computer-assisted technique was twofold: (1) it was aimed at decreasing both the human and technical sources of variability in measuring dispersion indices to leave the physiologic variability as unscathed as possible; and (2) it allowed analysis of a vast population of recordings, which was necessary for studying the distribution of these dispersion indices in various clinical groups.

So far, manual methods of QT interval measurement have mostly been used. These methods are tedious and time-consuming and are influenced by technical factors such as quality of tracings, artifacts and baseline noise, filtering techniques, etc., as well as by interobserver variability, which may amount to a 10–28-ms difference for the QT interval duration (9,28). Manual work has been somewhat facilitated by the use of digitizers and tracing enlargement. Thus, Bhullar et al. have developed a personal computer-based system for converting hardcopy ECGs to digitized records and automatically measuring QT interval dispersion from the digitized records (11). However, with the widespread availability of computerized electrocardiography, it is now possible to take full advantage of the speed, precision, and reproducibility of digital computers to obtain quantitative ECG measurements and from them to compute the DVR automatically. A few attempts have already been made to use digital computer systems to quantitate the ventricular repolarization (29–31). However, relying on a fully automated system may produce sizable measurement errors. Mc Laughlin et al. have recently compared four different algorithms for automatic QT interval measurement on the normal 12-lead ECG (32). They found that different QT measurement techniques produced variable results, which were influenced by filtering and technique variables. The mean automatic QT interval difference as related to the reference manual measurement was 62 ms, with a SD of 54 ms. Even after exclusion of the least reliable algorithm, the range of mean automatic QT differences was still 40 ms.

Furthermore, the nonuniform distribution of automatic QT differences across the different ECG leads implies that dispersion values may be higher for automatically determined QT intervals. This is why we decided to design a system that would combine the advantages of the two manual and automatic methods for the quantitation of ventricular repolarization.

The choice of 15-lead recordings, with the corrected Frank orthogonal lead system being used to identify the global fiducial points of the QRS-T complex, was based on theoretical and practical considerations. The interlead variability in QT measurements is due mainly to variability in timing of the T wave offset rather than to the onset of the QRS complex. The interlead variations in the onsets and offsets of waves and deflections may be due to the existence of isoelectric segments that correspond to a perpendicular (90°) orientation of the spatial depolarization or repolarization vectors to a particular lead orientation. Thus, the variation in QT measurements between leads is partly due to

differing orientations of these leads to a single repolarization vector. The problem is to be able to make the distinction between these "projection effects" and the interlead inequality due to a real pathophysiologic phenomenon, such as fragmentation or heterogeneity of the recovery wavefront within the myocardium. The choice of a lead or a lead subset is thus a major determinant of the accuracy of the QT interval estimates. Cowan et al. (10) and the CSE Working Party (13) have shown that in the 12-lead ECG, the QT interval was most accurately measured in the precordial leads V_1 to V_3, with these leads displaying the least variability. Others have advocated the use of all six precordial leads or only lead V_5. Zareba et al. have suggested that three pseudoorthogonal leads, such as I, aVF, and V_2, were sufficient to substantiate 12- or 6-lead configurations in order to identify patients with an increased dispersion of repolarization (23).

Our data showed a relationship between QT dispersion and the leads, reflecting a pathologic process. The lower dispersion observed in inferior versus anterior MIs could be partly the result of under-representation of the inferior wall in the ECG. As shown in Table 3, the dispersion values were higher in leads II, III, and aVF in inferior MI patients, while they were higher in the precordial leads in anterior MI patients, which suggests that it might be interesting to consider a lead-dependent distribution of the ECG indices of DVR. We thought that the Frank orthogonal three-lead system would be the most suitable to provide a single accurate global measure of the QT and JT intervals. Indeed, the corrected orthogonal lead system was specifically designed to pick up the dipolar content of the ECG while being less influenced than any subset of conventional ECG leads by these projection or "proximity" effects. Sylven et al. showed that the average QT duration computed from the orthogonal Frank leads correlated highly with the average QT duration measured from 120-lead body surface mapping (15). Zywietz et al. of the CSE Working Party found that the orthogonal three-lead systems that performed beat averaging and 2-ms sampling displayed the least variability and the best reproducibility for quantitative measurements (33). Therefore, we decided to incorporate the three Frank XYZ leads in the measurement of repolarization dispersion, to derive from them the global assessment of the fiducial points, and to transpose these points onto the whole synchronously recorded 15-lead system. Our data proved (Table 3) that the XYZ-lead subset contained the highest discriminant power, with the best separation of the ECG indices of dispersion between normal and MI patients.

This conclusion suggests that the global spatial information present in the XYZ leads is sufficient for accurate measurement of the dispersion of ventricular repolarization. It also implies that the largest mean values and ranges of the ECG indices of dispersion displayed by the 12 conventional leads might be partly related to a technical artifact (eg, tangential orientation of repolarization vectors in contiguous unipolar or bipolar leads) and not entirely due to a pathophysiologic mechanism. Through the interactive editing procedure, three successive screens display these global limits, and by moving a cursor, the observer can then modify the exact location of the J point and T endpoint in each individual lead. The editing procedure, which takes only a few minutes, is immediately followed by the automatic computing of various indices of repolarization dispersion. To be included in the statistical analysis, a single 15-lead record must have at least 10 leads from which the T wave end is clearly identifiable. No lead adjustment formula was used (eg, dividing the QT dispersion by the square root of the number of measurable leads or using the coefficient of variation of QT intervals for all measured leads). It has recently been shown that these lead adjustment formulas were not appropriate in healthy subjects (34) or in patients with MI (35), since they produce larger differences in the dispersion values.

As has most often been done in previous studies on QT dispersion, all the values reported in this study were corrected according to heart rate by means of Bazett's formula (15). However, introducing a rate correction factor is probably not necessary in assessing the dispersion of ventricular repolarization. In the whole group of 1,000 normal subjects, no significant correlation was found between the QT dispersion and the heart rate over a range of 45–125 beats/min. There was no influence of the correction factor ($\sqrt{RR}$) on the QT dispersion values. The correlation between QTc and QT dispersion was highly significant ($r = .98$, $P < .001$). The same conclusions could be drawn by looking at the correlation between QT dispersion and heart rate, between $\sqrt{RR}$ and QT dispersion, and between QT and QTc in three subsets of heart rate (< 60 beats/min, > 80 beats/min, and 60–80 beats/min) in normal subjects and also in the two MI groups. Thus, the rate correction is probably unnecessary in the assessment of DVR, although substituting QTc for QT probably does not introduce an additional source of error.

Normalization of Dispersion of Repolarization

Before assessing the predictive value of an increased DVR in individual cases, it is necessary to know the standard limits of the ECG indices of dispersion in normal subjects as well as in various clinical groups free of ventricular arrhythmias. There have been few published data about the magnitude of dispersion in subjects belonging to various clinical groups and on the prevalence of increased dispersion in the patients in whom arrhythmic events are present. According to Surawicz, the DVR in a normal subject probably does not exceed the interval going from the apex of the T wave (recovery of excitability at the earliest site of repolarization) to the end of the T wave (true end of repolarization)—that is, 70–90 ms (2). Mirvis found that the dispersion of QT interval in precordial maps ranged from 34 to 88 ms in a series of 50 normal subjects (26). In the same setting, Sylven et al. found that dispersion of repolarization averaged 89 ms in normal subjects and 155 ms in 14 patients with prolonged QT interval (25), Merri et al. showed, by computerized quantitation of repolarization, that heterogeneity of recovery expressed as the standard deviation of the J point–T apex interval in precordial leads was similar in 200 normal women and in 223 normal men (18.7 and 16.9 ms, respectively), whereas there were significant sex differences in the mean values of this parameter (222 ms in women and 205 ms in men) (29). Sedgwick et al. recorded monophasic action potentials on endocardial contact catheter recordings and found values of QT dispersion ranging from 30 to 50 ms in patients with stable angina pectoris (36). Cowan et al. found that the QT dispersion computed on the 12-lead ECG was small in a group of subjects without cardiac disease (48 ± 18 ms), as compared with patients after acute MI (anterior MI, 70 ± 30 ms; inferior MI, 73 ± 32 ms) (10). Zareba et al. showed by multivariate analysis that two dispersion indices, JTe and QRS duration, were predictive of arrhythmic cardiac death in patients with coronary artery disease (4). The mean JTe dispersion was 59 (± 20 ms) in patients surviving versus 82 (± 26 ms) in those dying. Of the patients who died, 82% had either a JTe dispersion of 80 ms or greater or a QRS duration of 95 ms or longer.

In a recent report, Pye et al. found that there was a significantly greater QT dispersion in patients with sustained ventricular arrhythmias than in control patients without arrhythmia (77 vs 38 ms), and this held true for three groups: patients who have had MI (82 ± 22 ms vs 38 ± 10 ms), those with dilated cardiomyopathy (76 ± 18 ms vs 40 ± 11 ms), and those without structural heart disease (65 ± 7 ms vs 32 ± 8 ms) (5). In 44 patients with chronic heart failure secondary to ischemic heart disease, Barr et al. observed that the QTc dispersion was significantly higher in sudden cardiac death patients (98.6 ± 19.4 ms) than in patients dying from progressive heart failure (66.7 ± 14.9 ms) and in survivors (53.1 ± 11.2 ms) (37).

Perkiömäki et al., in a study of QT interval dispersion in patients with and without susceptibility to ventricular tachyarrhythmias after MI, found that the QTc dispersion was significantly increased in patients with susceptibility to arrhythmias (104 ± 41 ms) as compared with that both in healthy subjects (38 ± 14 ms) and in postinfarction patients with no susceptibility to arrhythmias (65 ± 31 ms) (38). Tieleman et al. found that QT dispersion was increased in patients with mitral valve prolapse and ventricular arrhythmias (60 ± 20 ms) as compared with matched control subjects (39 ± 11 ms) (39).

All these previous studies were based on small series of patients with case-control or cross-sectional design. Zareba et al. have emphasized the need for further large studies, particularly with an automatic observer-independent analysis of dispersion to verify the real clinical usefulness of this parameter (23). In a recent editorial, Higham and Campbell wrote that the normal QTc dispersion values measured by digitizer are 20–50 ms in normal subjects, rising to 60–100 ms after infarction and as high as 150–200 ms in the long QT syndrome (7). Our study was the first to use a computer-assisted method to assess the norms of various ECG indices of DVR in a large clinical group, including normal subjects as well as patients with various cardiac abnormalities but without history of ventricular arrhythmias and without drug interaction. In the group of 1,000 normal subjects, there was no significant correlation between any of the dispersion indices and either age or sex. Thus, age does not seem to influence the DVR: a given value can be observed in all age categories from 20 to 80 years, and normal subjects of the same age can have very different values within the normal range. Similarly, no significant difference was found between men and women. These results held true when we analyzed the various pathologic groups; there was no indication that the results should be stratified according to age and sex.

For all the dispersion indices analyzed (QTe, JTe, QTa, JTa), the mean values, standard deviations, and

percentile ranges were significantly higher in pathologic groups than in healthy subjects. With a few exceptions, no significant difference was found between the pathologic groups themselves (Table 2).

The two most discriminant dispersion indices were those expressing the dispersion of the global repolarization (ie, QTe and JTe), which exhibited significantly lower distribution values in the normal group than in all pathologic groups. The QTa and JTa, which represent the early part of the repolarization, had smaller values in normal subjects than in pathologic groups, except for patients with inferior MI, which was close to normal. For the index related to the late part of the repolarization, Ta-Te, the dispersion values were lower in normal subjects as compared with only two pathologic groups—patients with left ventricular hypertrophy and those with intraventricular conduction defect.

Generally, the distribution curves of the various ECG dispersion indices exhibited an approximate bell shape in the normal population, whereas those of the pathologic groups, especially the MI patients, showed a somewhat bimodal pattern and were shifted to the right (Figs. 3, 4).

A practical implication would be the need to define different standard limits of the ECG dispersion indices according to the clinical group to which a given individual belongs. For instance, the upper standard limit, corresponding to the 97.5th percentile of QTe and JTe dispersion, would be 65.3 and 75.8 ms, respectively, in normal subjects; 84.5 and 86 ms after inferior MI; 89.5 and 99.8 ms after anterior MI; 90 and 98 ms in patients with left ventricular hypertrophy; and 93.7 and 99.1 ms in those with intraventricular conduction defects.

The two most relevant clinical findings of our computer-assisted study of various ECG dispersion indices in various clinical groups are as follows: (1) a significantly increased DVR is associated with all the pathologic entities considered in this study, even in the absence of documented ventricular arrhythmias; and (2) individual measurements of the DVR taken as predictors of future arrhythmic events should be referred to the range defined as standard for their appropriate clinical group. We intend to continue our research on the clinical usefulness of the DVR along two lines: by comparing, in retrospective studies, the value of various ECG indices of DVR in patients with a history of ventricular arrhythmia against the standard range of their own clinical group; and by launching a prospective study to analyze the prognostic value of these dispersion indices, especially in patients with coronary heart disease.

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