

Dispersion of QT and QRS in Patients with Severe Congestive Heart Failure: Relation to Cardiac and Sudden Death Mortality

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Introduction: Death in patients with severe congestive heart failure (CHF) occurs either by progressive pump failure or suddenly. There is increasing evidence that pronounced variability of ventricular repolarization (QT dispersion) might predict excessive mortality risk. However, no data exist regarding variation of intraventricular conduction (QRS dispersion) and cardiac and sudden death mortality. The aim of this study was to examine the relation of QT and QRS dispersion to cardiac and sudden death mortality in a group of 104 patients with severe CHF.

Methods: One hundred and four patients, aged 53 ± 13 years, in NYHA class II to IV, with ventricular ejection fraction $<35\%$, were followed prospectively. QT and QRS dispersion was defined as the difference between maximum and minimum QT and QRS duration respectively, measured in 12-lead electrocardiograms. The end-points of the study were non-sudden and sudden cardiac death.

Results: During a 20-month period of follow-up there were 13 non-sudden and 10 sudden deaths. QT and QRS dispersion was significantly longer in non-survivors than in survivors (95 ± 48 msec vs. 78 ± 31 msec, $P < 0.03$ and 54 ± 17 msec vs. 46 ± 16 msec, $P < 0.02$, respectively). Furthermore, patients who died suddenly had significantly greater QRS dispersion than those who survived (56 ± 13 msec vs. 46 ± 16 msec, $p < 0.02$). In a multivariate regression analysis, QT and QRS dispersion were identified as independent predictors of cardiac death ($P = 0.01$ and $P = 0.001$, respectively) while QRS dispersion was also an independent predictor of sudden cardiac death ($P = 0.04$).

Conclusions: QT and QRS dispersion are useful predictors of mortality in patients with severe congestive heart failure.

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In the last few years, QT dispersion constitutes an intensively studied, possible prognostic factor of arrhythmic and, in general, cardiac risk as regards patients suffering from various heart diseases. High values of QT dispersion reflect an inhomogeneity of the repolarization time of the ventricular myocardium that may be the substrate for the development of malignant ventricular arrhythmias^{1,2}. At the same time, pharmaceutical agents with a proven anti-arrhythmic effect, such as sotalol and amiodarone, seem to reduce this dispersion^{3,4}.

In coronary artery disease, a reduction of the QT dispersion was observed following successful thrombolytic treatment in patients with acute myocardial infarction⁵. To the contrary, high QT dispersion values were correlated with increased risk of life threatening arrhythmias in patients who have survived an acute infarct^{6,7}. However, in a recently published study, this same parameter did not constitute a predictive factor for mortality or for arrhythmic events in a similar population of patients⁸.

Contrary to coronary artery disease, the existing data on the usefulness of QT

dispersion in patients with chronic congestive heart failure are very limited⁹⁻¹¹. The possible prognostic value of QRS dispersion in the 12-lead ECG in such patients has not even been studied.

Thus, the aim of the present study is to investigate the possible prognostic value of QT and QRS dispersion in predicting mortality risk in patients with severe congestive heart failure and to correlate the measurements of QT and QRS dispersion with other known prognostic factors of dysfunction of the left ventricle that predict increased mortality.

Patients and methods

The study population consisted of patients suffering from heart failure as a result of coronary artery disease or of dilated cardiomyopathy, of NYHA II to IV functional class and of an ejection fraction of <35%, who were followed-up at the heart failure outpatient clinic of the Department of Clinical Therapeutics of the University of Athens. Patients >75 years old, with heart failure of other etiology, renal failure (creatinine >3 mg/dl), recent (within the last three months) myocardial infarction or heart surgery, were not included in the study, nor were included patients presenting electrolyte disorders or receiving amiodarone or b-blockers, since these agents are known to affect QT values. The protocol was approved by the Department of Clinical Therapeutics of the University of Athens.

Electrocardiogram measurements

Twelve-lead electrocardiograms were measured, recorded at a speed of 25 mm/sec, taken upon entry of the patients in the study. The analysis was performed by one investigator only. QT, QRS and RR measurement was performed with the use of computer software (Configurable Measurement System) using digitizer 9000 (Calcomp, Anaheim, California).

The QT interval was measured from the start of the QRS complex up to the end of T wave, that is to the point where T wave returned to the isoelectric line. In case there was a U wave, the QT interval was measured to the lowest part of the curve between the T and U waves.

The QRS interval was measured from the start of the Q wave or in absence of the Q wave, from the start of R wave to the end of S, that is to its return to the isoelectric line.

We did not measure the JT interval; it was calculated, however, as the QRS-QT difference for every QRS interval measured.

In each electrocardiogram lead, the analysis included 3 consecutive heart cycles, whenever possible. We did not assess QT intervals in the cases where the end of the T wave could not be clearly determined, either due to its morphology or due to particularly low potentials.

QT dispersion was defined as the difference between maximum and minimum QT intervals, measured in electrocardiograms in which at least 6 leads were appropriate for analysis.

The difference between maximum and minimum JT intervals was defined as *JT dispersion* and similarly, the difference between the narrower and the wider QRS interval was defined as the *QRS dispersion*.

Clinical and other laboratory data

Patients were clinically assessed and their NYHA class recorded. Left ventricular dimensions (end-diastolic and end-systolic diameters) were assessed by ultrasound, while the left ventricular ejection fraction was measured with radioisotopic ventriculography with technetium-99 labeled red blood cells.

Follow-up

Enrollment of patients in the study began in June 1993 and was completed by July 1997. Patients were prospectively followed-up for 20 ± 12 months. The primary end-point was all-cause mortality and the second end-point was sudden cardiac death that was defined as death within one hour from the onset of new symptoms on a previously clinically stable patient.

Statistical analysis

The data were presented as mean values, as medians and as 25% and 75% percentiles. A multivariate analysis was performed using the Cox proportional hazard regression model. Multiple variates, i.e demographic (age, gender), clinical, (coronary vs. non coronary etiology, NYHA class), laboratory (radioisotopic ejection fraction, end-systolic and end-diastolic diameters) and electrocardiographic parameters (minimum QT, maximum QT, mean QT, QT dispersion, minimum QRS, maximum QRS, mean QRS, QRS dispersion, minimum JT, maximum JT, mean JT, JT dispersion) were initially assessed regarding their univariate correlation

Table 1. Main patient characteristics among the three outcome groups.

Mean/Median values (Range)	Survivors (N=81)	Non-survivors (N=23)	Sudden death (N=10)
Demographics			
Age (yrs)	51/53 (45-60)	57/55 (50-65)	53/55 (48-62)
Sex (male) (%)	68 (84)	19 (83)	8 (80)
Underlying disease: coronary artery disease (%)	33 (41)	12 (52)	5 (50)
NYHA: III or IV (%)	26 (32)	15 (65)	4 (40)
LV ejection fraction (%)	24/24 (16-32)	17/15 (11-24)	15/13 (10-23)
Follow-up duration (mo)	23/23 (14-36)	9/5 (0,7-15)	16/13 (6-28)
ULTRASOUND			
End-diastolic dimension (mm)	70/70 (64-75)	69/68 (62-77)	70/72 (64-79)
End-systolic dimension (mm)	56/57 (50-62)	54/55 (47- 62)	57/57 (50-63)

with the time of death. Variates for which $P < 0.1$, composed a multivariate analysis model for the evaluation of the independent correlation of each of them with the event (cardiac mortality or sudden death). We also used Kaplan-Mayer survival curves to compare survival of groups that were of specific interest.

Analyses were performed using the statistical package SPSS 6.1 software. $P < 0.05$ (2-tailed) was considered to be statistically significant.

Results

The demographic and electrocardiographic characteristics of the 104 patients who met the study inclusion criteria are presented in Tables 1 and 2. There are 87 men and 17 women, aged 52.6 ± 12.9 years; the underlying cause of heart failure was dilated cardiomyopathy in 59 patients and coronary artery disease in the other 45 patients. The average radioisotopic

Table 2. Electrocardiographic variables among the outcome groups.

Mean/Median values (Range)	Survivors (N=81)	Non-survivors (N=23)	Sudden death (N=10)
Analyzable no. of leads	9,6/10 (8-11)	9,2/10 (7-11)	9,8/11 (7-12)
QT VARIABLES			
QT dispersion	78/74 (58-94)	95/86 (57-127)	69/73 (48-88)
Average QT	375/367 (339-413)	378/384 (326-415)	391/387 (332-465)
Minimum QT	335/323 (302-366)	333/321 (293-375)	357/351 (307-426)
Maximum QT	413/401 (372-451)	428/429 (362-493)	426/429 (363-496)
JT VARIABLES			
JT dispersion	73/66 (52-89)	98/87 (61-138)	80/81 (57-95)
Average JT	261/254 (238-280)	251/247 (219-284)	250/247 (219-284)
Minimum JT	225/216 (200-246)	202/195 (183-225)	219/227 (181-252)
Maximum JT	298/290 (267-320)	301/286 (262-327)	298/295 (263-319)
QRS VARIABLES			
QRS dispersion	46/44(36-55)	54/51(43-63)	56/57(48-70)
Average QRS	113/103(85-135)	125/124(94-156)	132/129(94-162)
Minimum QRS	87/76(60-110)	95/90(70-113)	100/89(75-126)
Maximum QRS	133/123(107-158)	149/140(117-178)	156/150(116-118)
Bundle branch block or intraventricular conduction defect (%)	16(20)	7(30)	5(50)

Table 3. Univariate predictors of cardiac death and sudden death.

Cardiac death			Sudden death		
Variables	χ^2	p value	Variables	χ^2	p value
NYHA: I or II vs III or IV	8,07	0,005	BBB or intraventricular conduction defect	8,20	0,0004
JT dispersion	7,97	0,005	Maximum QRS	6,82	0,01
Minimum JT	5,97	0,01	Average QRS	5,71	0,02
QRS dispersion	5,28	0,02	QRS dispersion	5,09	0,02
Maximum QRS	5,49	0,02	LV ejection fraction	4,00	0,04
LV ejection fraction	4,52	0,03	Minimum QT	3,09	0,08
QT dispersion	4,69	0,03	Minimum QRS	2,62	0,10
Average QRS	4,18	0,04	Average QT	1,67	0,20
BBB or intraventricular conduction defect	2,58	0,11	QT dispersion	1,10	0,29
Minimum QRS	1,84	0,17	Maximum QT	0,66	0,41
Age (yrs)	1,62	0,20	No. of leads	0,30	0,58
Maximum QT	1,49	0,22	End-systolic dimension (mm)	0,27	0,60
Average JT	1,33	0,25	End-diastolic dimension(mm)	0,14	0,70
No. of leads	0,73	0,39	Age (yrs)	0,13	0,72
CAD vs non-CAD	0,43	0,51	Minimum JT	0,12	0,73
Average QT	0,26	0,62	Average JT	0,08	0,78
End-systolic dimension (mm)	0,21	0,65	JT dispersion	0,04	0,84
Maximum JT	0,01	0,91	NYHA: I or II vs III or IV	0,04	0,84
Men vs women	0	0,97	Men vs women	0,02	0,87
End-diastolic dimension (mm)	0	0,97	CAD vs non-CAD	0,02	0,88
Minimum QT	0	0,98	Maximum JT	0,02	0,89

ejection fraction was $22 \pm 10\%$. The NYHA functional class was 2.24 ± 0.85 and, more specifically, 18 patients (17%) belonged to class I, 45 (43%) to class II, 33 (32%) to class III and 8 (8%) to class IV. The mean follow-up was 20 ± 12 months (from 0.43 to 36 months). They were all on angiotensin converting enzyme inhibitors, digitalis and diuretics.

Outcome

Of a total of 104 patients, 23 died within the follow-up period, of whom 10 by sudden death. No death was attributed to non-cardiological causes.

Clinical and laboratory parameters

Among the assessed clinical parameters that included age, gender, etiology of heart failure and NYHA functional class, the latter was shown to be the most potent prognostic factor of cardiac ($P = 0.005$), but not

of sudden death ($P = 0.84$) (Table 3). Among the laboratory parameters, left ventricular ejection fraction, emerged as a prognostic factor both of cardiac mortality regardless of the cause ($p = 0.03$), as well as of sudden death mortality ($p = 0.04$), despite its overall particularly low value (Table 3). To the contrary, none of the echocardiographic parameters did predict mortality.

Repeatability of measurements

Repeat measurements of QT dispersion were performed on 25 randomly chosen electrocardiograms by the same observer. The variability of the measurements was 0.36 ± 15 msec, non statistically significant. The standard correlation was 95% (95% confidence intervals -6.73 to 6.01). Similar measurements took place with regard to QRS dispersion on 17 also randomly chosen electrocardiograms. Likewise, the variability was not statistically significant ($1.35 \pm$

15msec) with a 64% standard correlation (95% confidence intervals -9.15 to 6.44).

Electrocardiographic analysis

QRS and QT intervals were measured in 11±1 leads (from 8 to 12 leads) and in 10±2 leads (range: 6 to 12 leads), respectively. The mean values for QRS, QT and JT intervals were 115±34 msec, (range: 67 to 202), 376±50 msec (range: 278 to 510), and 259±40 msec (range 175 to 378), respectively. The mean value of the maximum QT interval was 416±58 msec (range 301 to 550), whereas the mean value of the minimum QT interval was 334±48 msec (range 244 to 485). The mean value of QT dispersion was 82±36 msec (range 29 to 221).

With regard to QRS interval, the mean value of the maximum QRS was 136±36 msec (range 85 to 234), the mean value of the minimum was 89±33 msec (range: 42 to 188) while the mean QRS dispersion was 48±16 msec (range: 13 to 103).

Finally, for the JT interval, the mean value of the maximum JT was 299±50 msec (range: 189 to 462), the mean value of the minimum JT was 220±39 msec (range: 140 to 329) while the mean JT dispersion was 79±38msec (range: 13 to 228).

Electrocardiographic analysis and outcome

Significant difference was observed in the QT dispersion of patients who *survived* vs. patients who *died* of heart problems, but not vs. those who died suddenly. Thus, the mean value of QT dispersion

was 78±31msec for survivors against 95±48msec for non-survivors and against 69±21msec for patients who died suddenly (P=0.03 and P=0.29, respectively, tables 2 and 3). When patients were divided in two groups, those with QT dispersion ≤90 msec against those with >90 msec, total mortality in the three years was different for the two groups (17% versus 31% respectively, relative risk 2.8, 95% confidence intervals 1.2 to 6.4, figure 1). When the above two groups were examined regarding age, gender, etiology of heart failure, NYHA functional class, ejection fraction and left ventricle diameters, no differences were observed between them.

We observed similar results with JT dispersion with significant differences between patients who survived (73±34 msec), against those who died from any cardiac cause (98±46 msec, P=0.005) (Tables 2 and 3). Moreover, significant differences were also measured in QRS dispersion between patients who survived (46±16 msec), and those who died from any cardiac cause (54±17 msec) and also those who died suddenly (56±13 msec), respectively (P=0.02 for both, tables 2 and 3). When the patients were divided in two groups, one with QRS ≤46 msec and the other with QRS >46 msec, the difference in the three years mortality was significant (13% versus 32%, relative risk 3.85, 95% confidence interval 1.6 to 9.5, figure 2). In this case too, the groups did not differ significantly as regarded demographic, clinical and laboratory characteristics (age, gender, heart failure etiology, ejection fraction, NYHA functional status).

We then proceeded to a comparison of survival of the 14 patients who presented QRS dispersion >46

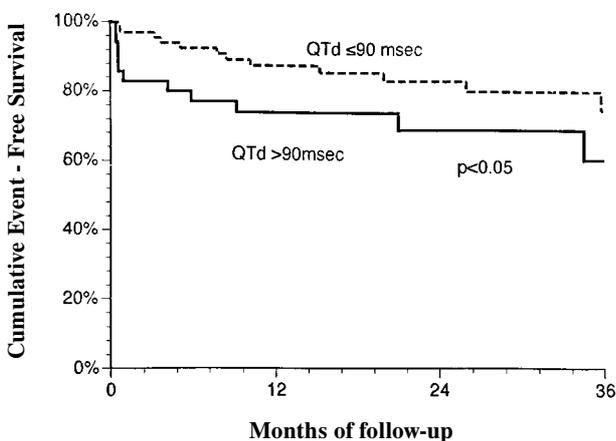


Figure 1. Cumulative event-free survival in patients with severe congestive heart failure and QTd ≤90 msec (n=69) versus those with QTd >90 msec (n=35) during the 3 years of follow-up.

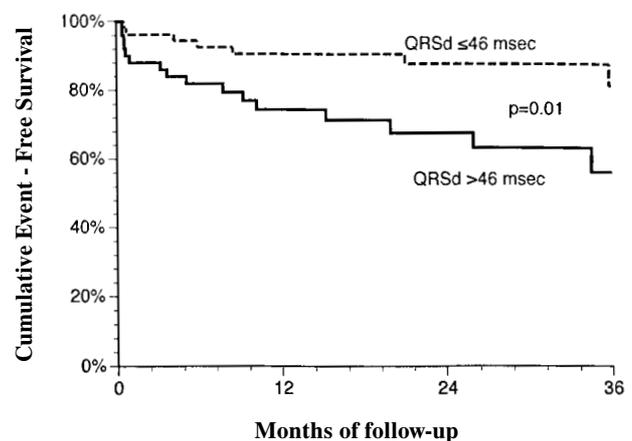


Figure 2. Cumulative event-free survival in patients with severe congestive heart failure and QRSd ≤46 msec (n=54) versus those with QRSd >46 msec (n=50) during the 3 years of follow-up.

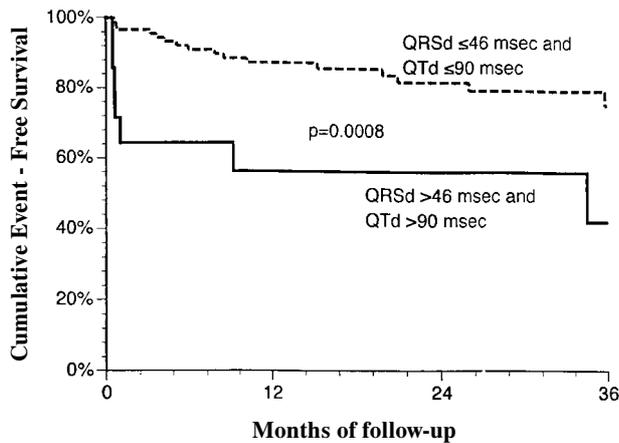


Figure 3. Cumulative event-free survival in patients with severe congestive heart failure and QRS (QRSd) ≤ 46 msec and QTd ≤ 90 msec (n=90) versus those with QRSd > 46 msec and QTd > 90 msec (n=14) during the 3 years of follow-up.

msec and QT dispersion > 90 msec versus the remaining 90 patients with QRS dispersion ≤ 46 msec and QT dispersion ≤ 90 msec. Survival in 36 months was 50% against 82% respectively (P=0.0008, figure 3).

His bundle branch block that was defined as QRS duration ≥ 120 msec or disorder of intraventricular conductivity was observed in 16 survivors (20%), 7 patients (30%) who died of cardiac etiology and 5 patients (50%) who died suddenly (P=0.11 and P=0.004, respectively, tables 2 and 3).

In a multivariate analysis model that was constructed to examine the relative value of QT and QRS dispersions compared to clinical parameters, the following independent prognostic factors of total cardiac mortality were found: NYHA functional class (P=0.0007), QRS dispersion (P=0.001) and QT dispersion (P=0.01). Furthermore, His bundle branch block and intraventricular conductivity disorders (P=0.02), as well as QRS dispersion, (P=0.04) were found to be prognostic factors of sudden death.

Discussion

The results of the present study suggest increased mortality risk of patients with severe congestive heart failure, who present significant dispersion in repolarization of ventricular myocardium^{12,13}. Additionally, and for the first time, we assessed the possible correlation of the dispersion of the intraventricular conduction velocity (QRS dispersion) with the mortality of such patients. Thus, high QRS dispersion, in 12-lead electrocardiograms, was a predictive

factor of increased risk for cardiac, as well as sudden, death. More specifically, the group of patients with QT dispersion > 90 msec and QRS dispersion > 46 msec presented significantly increased risk of death, against patients with QT dispersion ≤ 90 msec and QRS dispersion QRS ≤ 46 msec.

The death of patients who suffer from congestive heart failure comes either progressively¹⁴, due to deterioration of the dysfunction of the left ventricle or suddenly and unexpectedly^{15,16}. Several studies have indicated various prognostic risk factors such as low ejection fraction, high NYHA class, limited exercise tolerance, hypomagnesemia and increased levels of neurohumoral stimulation^{17,18}. The possible relationship between the heterogeneity in ventricular repolarization that is expressed through QT dispersion of such patients and the mortality risk has not been clarified.

Previous studies have shown that the QT dispersion is a sufficient prognostic factor of sudden death in chronic heart failure⁹, as well as in hypertrophic cardiomyopathy with ventricular arrhythmia¹⁹. The present study demonstrated that high QT dispersion values were prognostic indicators for cardiac but not sudden death. Such data agree with the respective results by Pinsky et al²⁰ in a population of heart transplant candidate patients. The mean value of the QT dispersion of non-survivors was 112 msec versus 95 msec in our own group, that may be due to the higher severity of those patients. QT dispersion did not predict mortality nor arrhythmic events in patients following myocardial infarction⁸. However, the population of that study is different from our own. Aside from the heterogeneity in repolarization, heterogeneity in conductivity is also proven to be a prognostic factor for death. Thus, patients with QRS dispersion > 46 msec presented 3.8 times higher mortality risk, against patients with values ≤ 46 msec. Additionally, this parameter also predicted sudden death, i.e. patients who had values higher than 46 msec had 4.8 times higher risk. The fact of heterogeneity in the QRS duration between several electrocardiogram leads has not been reported in the past for heart failure patients.

Limitations of the study

QT interval measurements were conducted in 12-lead ECGs, with the use of computer software and digitizer by an experienced observer. Despite all that, the reliability of the measurements remains

uncertain to the extent where the lack of a consensus has as a consequence the absence of indisputable, generally accepted criteria for the definition of the end of T interval. Yet, since the mean variability of the observer's measurements was in the range of 0.36 msec, the differences in QT dispersion cannot be attributed to it.

The categorization of patients into groups depending on QT dispersion with QT >90 msec versus ≤90msec and QRS dispersion >46 msec versus ≤46 msec was done retrospectively and, consequently, the results have to be verified prospectively.

Finally, the present study included patients with severe left ventricular dysfunction, possible heart transplantation candidates. Thus, the results cannot be extended to patients with less severe heart failure.

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