Effect of *Amiodarone* on the Descending Limb of the T Wave

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Comparing patients treated after myocardial infarction with amiodarone or with placebo, we found a significant rate-dependent prolongation of TpTe interval in patients who received amiodarone. Patients who had arrhythmic death had significantly longer TpTe intervals than others on placebo but not on amiodarone. Assuming that TpTe reflects transmural repolarization heterogeneity, our findings suggest that heterogeneity and arrhythmic risk are increased by amiodarone. This contradicts the finding of decreased transmural repolarization heterogeneity by amiodarone and the appreciated antiarrhythmic efficacy of this drug. **(Am J Cardiol 2003;92:742–746)**

There are substantial differences in the electrical properties between different layers of the ventricular myocardium.[1] Based on in vitro experiments, the interval between the peak and the end of the T wave (TpTe) was proposed to quantify transmural heterogeneity in action potential duration (APD).[2] Also based on in vitro experiments, the antiarrhythmic effect of amiodarone was partly attributed to decreased transmural repolarization heterogeneity.[3] However, there is no evidence that this drug has this effect in the clinical setting. We therefore examined the following assumptions. (1) If TpTe expresses transmural repolarization heterogeneity and if amiodarone decreases this heterogeneity, will the TpTe intervals in patients receiving placebo after infarction be longer than in those receiving amiodarone? (2) If the antiarrhythmic effect of amiodarone is at least in part achieved by the decrease of transmural repolarization heterogeneity, will patients who experience arrhythmic death while receiving amiodarone have longer TpTe intervals than those who do not? We therefore investigated QT, Q to T peak (QTp), and TpTe intervals in Holter recordings of patients who were enrolled into the European Myocardial Infarction Amiodarone Trial[4] (i.e., patients randomized to placebo and amiodarone after infarction).

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The study used data collected during the European Myocardial Infarction Amiodarone Trial.[4] In short, enrolled patients were survivors of acute myocardial infarction (aged 18 to 75 years) who had left ventricular ejection fraction ≤40% as assessed by multiple-gated nuclear angiography between days 5 and 21 after the index infarction. The median follow-up of the trial was 21 months. A total of 866 3-lead Holter recordings (462 from patients receiving amiodarone and 404 from patients receiving placebo) obtained 1 month after treatment randomization were available for this study. Clinical characteristics of the study population are listed in Table 1.

RR, QT, and QTp intervals in all 24-hour recordings were automatically measured on a beat-to-beat basis by a commercial Holter system (Pathfinder, Del Mar Reynolds Medical, Irvine, California). TpTe intervals were computed as the difference of QT and QTp intervals. The automatic measurement was performed under careful visual control, and artifacts were eliminated manually. Only beats with accepted QT and RR intervals were considered. In each recording, the analysis was performed using the lead with most accepted measurements.

Instead of using only the RR interval preceding each beat, weighted averages of RR intervals ($\overline{RR}$) within a window preceding each beat were considered. Using a previously described technology,[5] cardiac cycles in a window previous to the QT measurement were weighted for their impact on its rate adaptation. For each cardiac beat, the corresponding numeric representation of the RR interval history and the corresponding $\overline{RR}$ interval value was derived. The optimum averaging window was identified individually in each patient by best-fitting QT/$\overline{RR}$ data to a set of 10 a priori defined regression models designed to cover a physiologic variety of QT/RR patterns.[6] In this way, the influence of QT/RR hysteresis on the assessment of the QT/RR relation was eliminated.

Because transmural repolarization heterogeneity is known to be influenced by cycle length,[1] uncorrected QT, QTp, and TpTe intervals and TpTe/QT ratios were averaged in each recording across 10-ms $\overline{RR}$ interval bins ranging from 550 to 1,150 ms.

Statistical analysis was based on the intention to treat at randomization. Arrhythmic death was used as the outcome event. The classification of the mode of death originally performed by the event committee of the trial was used. A comparison was also performed between patients who did and did not have arrhythmic death. Averaged values of QT, QTp, and TpTe in individual $\overline{RR}$ bins were pooled together in amiodarone- and placebo-treated patients. Student's *t* test for unpaired samples was used for the comparison. A p

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0002-9149/03/$–see front matter
doi:10.1016/S0002-9149(03)00845-2

TABLE 1 Baseline Characteristics of Patients*

Characteristics	Amiodarone n = 462	Placebo n = 404	p Value†
Age (yrs)‡	60 ± 10	61 ± 9	0.323
Men/women	391 (85)/71 (15)	345 (85)/59 (15)	0.754
Myocardial infarction	144 (31)	121 (30)	0.899
Angina pectoris	177 (38)	144 (36)	0.275
Hypertension	164 (35)	112 (28)	0.011
Diabetes	72 (16)	68 (17)	0.619
New York Heart Association Class			
I	223 (48)	213 (53)	
II	207 (45)	157 (39)	0.381
III	31 (7)	31 (8)	
Baseline measures‡			
Left ventricular ejection fraction (%)	31 ± 7	30 ± 8	0.468
Systolic blood pressure (mm Hg)	119 ± 17	118 ± 17	0.459
Diastolic blood pressure (mm Hg)	73 ± 11	74 ± 11	0.352
Heart rate (ms)	73 ± 14	73 ± 13	0.884
QRS duration (ms)	91 ± 19	91 ± 19	1.000
QT interval (ms)	389 ± 48	391 ± 47	0.694
Concomitant medication			
Thrombolytics	266 (58)	235 (58)	0.860
Digoxin	61 (13)	47 (12)	0.486
β blocker	198 (43)	200 (50)	0.050
Calcium antagonist	70 (15)	62 (15)	0.937
Angiotensin-converting enzyme inhibitors	260 (56)	219 (54)	0.542
Follow-up end points	n = 59 (13)	n = 53 (13)	0.879
Noncardiac death	11 (2)	8 (2)	0.688
Cardiac death	48 (10)	45 (11)	0.723
Nonarrhythmic death	30 (6)	19 (5)	0.256
Arrhythmic death	18 (4)	26 (6)	0.090

*Values in parentheses represent the percentage of the total number in each arm.
†p Value refers to comparison between amiodarone group and placebo group.
‡Mean ± SD.

value <0.05 was considered statistically significant. Data are presented as mean ± SD.

The rate relations of the QT and QTp intervals are shown in Figure 1, and the rate relation of the TpTe interval and TpTe/QT ratio in the investigated groups is shown in Figure 2. Because it is obvious from these figures that the difference between the groups is rate dependent, Table 2 shows the statistical evaluation of the QT, QTp, and TpTe intervals and the TpTe/QT ratio at 2 different $\overline{RR}$ interval bins (i.e., 550 to 560 ms and 1,140 to 1,150 ms, respectively).

QTp and QT intervals were longer in patients without arrhythmic death who received amiodarone. The difference was rate dependent as evidenced by being more marked at long RR intervals. However, patients with arrhythmic death who received amiodarone had shorter QTp intervals than did patients who received placebo. Although this was less obvious at short RR intervals, it became increasingly more marked at longer RR intervals (Table 2; arrhythmic death on amiodarone vs no arrhythmic death on placebo: 550 to 560 ms, $p = 0.216$, and 1,140 to 1,150 ms, $p = 0.005$, respectively). For patients receiving placebo, there was no significant difference between those with and without arrhythmic death at any $\overline{RR}$ interval bin.

Among patients receiving amiodarone, the TpTe interval did not significantly differ between those who did and did not have arrhythmic death. However, irrespective of the arrhythmic outcome, TpTe was significantly longer in patients receiving amiodarone compared with those receiving placebo, with the difference being more marked at slow heart rates. For patients receiving placebo, those having arrhythmic death showed significantly longer TpTe intervals at short $\overline{RR}$ intervals.

In patients without arrhythmic death, the ratio of the TpTe interval to QT showed no rate dependence in patients receiving amiodarone or those receiving placebo and was higher in patients receiving amiodarone. However, among the patients receiving amiodarone, those with arrhythmic death had a higher ratio than did those without arrhythmic death; the difference was statistically significant at slow heart rates. Thus, although QTp and TpTe were prolonged proportionally in patients without arrhythmic death who were receiving amiodarone, TpTe was relatively longer in those patients with arrhythmic death because of a relative decrease in the QTp interval.

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We found a significant rate-dependent prolongation of QTp and the TpTe interval in patients who received amiodarone after infarction who did not have arrhythmic death. Although patients who received placebo who had arrhythmic death had significantly longer TpTe intervals than those who did not have arrhythmic death, there was no significant difference among patients who received amiodarone.

Assuming that TpTe reflects transmural repolarization heterogeneity, these findings suggest that this heterogeneity is increased by amiodarone. This contradicts the finding of decreased transmural repolarization heterogeneity by amiodarone in cardiac tissue models.[3] Although direct in vivo evidence of this drug effect is missing, 2 other studies that investigated the electrophysiologic effects of amiodarone in isolated Langendorff-perfused rabbit hearts[7,8] also described no changes in dispersion of APD across the epicardial[7] or between various right and left ventricular endocardial and epicardial sites.[8] Thus, a marked increase in transmural repolarization heterogeneity by amiodarone seems unlikely.

It seems therefore questionable whether the TpTe interval measured in clinical Holter recordings reflects transmural repolarization heterogeneity. Using a canine ventricular wedge model, it was demonstrated[2] that the inscription of the T wave of the electrocardiogram stems mainly from differences in APD in different layers of the ventricular wall. It was shown that the peak of the T wave marks full repolarization of the epicardium, whereas the end of the T wave marks full repolarization of the M region. Therefore, in vitro TpTe interval was shown to measure transmural dispersion of APD.[2] By recording epicardial

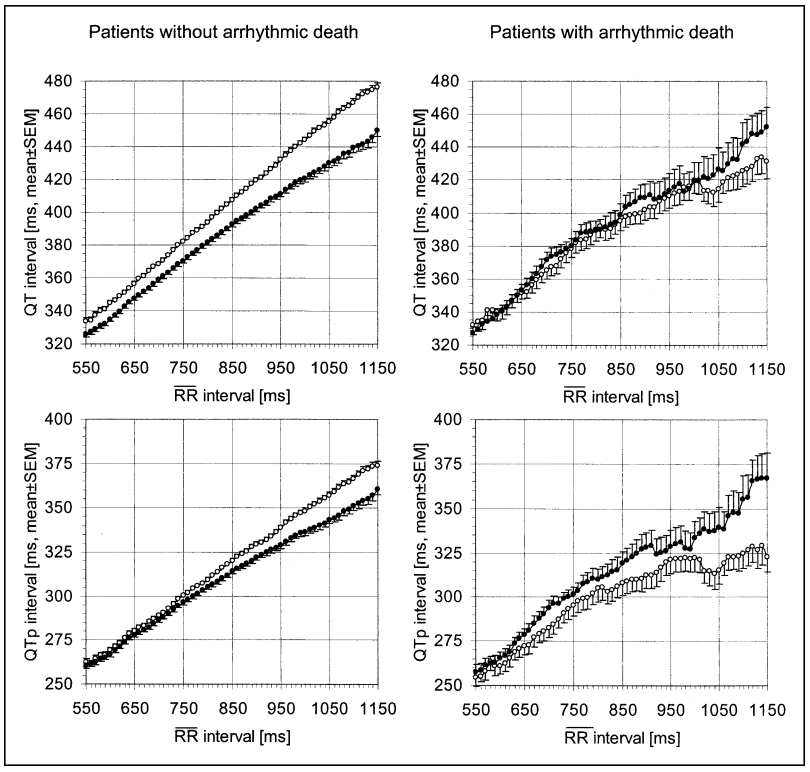

FIGURE 1. Uncorrected mean QT and QTp intervals in patients on amiodarone *(open circles)* or on placebo *(filled circles)* plotted against 10-ms RR interval bins. Comparison are made in patients with *(left panel)* and without *(right panel)* arrhythmic death.

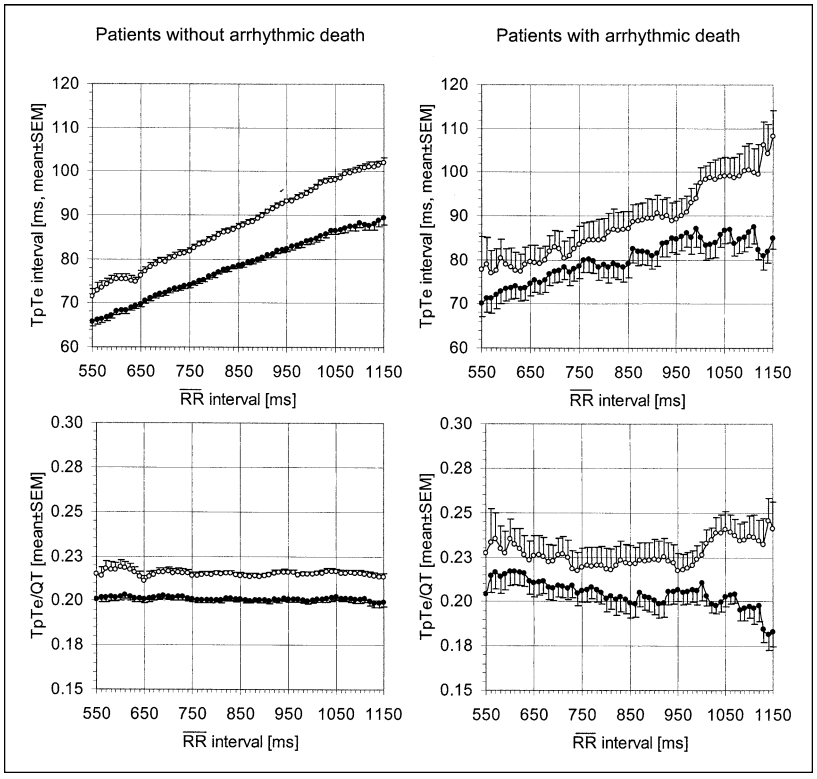

FIGURE 2. Uncorrected mean TpTe interval and TpTe/QT ratio in patients on amiodarone *(open circles)* or on placebo *(filled circles)* plotted against 10-ms RR interval bins. Comparison are made in patients with *(left panel)* and without *(right panel)* arrhythmic death.

monophasic action potentials from different areas of the heart in open-chested dogs simultaneously with 2 surface electrocardiographic leads, an earlier study[9] also suggested that TpTe interval bear a certain relation to the dispersion of repolarization in the entire heart.

Clinical evidence of this relation in humans is missing, and the extent of transmural gradients of APD in vivo remains to be established.[10,11] Additionally, recent evidence suggests that transmural heterogeneities might be even more variable than expected.[12] Considering the 3-dimensional structure of the intact heart and the multitude of gradients previously described[9,11,13,14] (e,g., apico-basal, right–left ventricular, anterior–posterior, and transmural), it seems unlikely, in a clinical setting, that the projection of the repolarization dipole onto the body surface could be attributed to just the transmural APD gradient. Still, although it was assumed already in the original study[2] that "the T wave measured in the intact organism is generated by more than transmural ventricular gradients," clinically measured TpTe intervals are being increasingly used as a surrogate of transmural repolarization heterogeneity.[15,16]

Clinical studies describing increased TpTe values in various high-risk populations[15–18] suggest that increased TpTe is, under some circumstances, related to arrhythmic risk. However, these observations do not prove that TpTe reflects transmural repolarization heterogeneity, and they also do not prove that increased TpTe is a general risk marker in each clinically defined population. Our finding of prolonged TpTe intervals in patients receiving amiodarone—together with the widely appreciated antiarrhythmic efficacy[4,19] and low proarrhythmicity[19,20] of the drug—is clearly not compatible with the notion that clinical TpTe measures transmural repolarization heterogeneity and that an increase in such a heterogeneity is an arrhythmic risk factor.

Viitasalo et al[16] recently described increased TpTe intervals in patients with long QT syndrome without a difference between symptomatic and asymptomatic patients. This challenges the association of

TABLE 2 QT, QTp, and TpTe Intervals and TpTe/QT Ratio at Different RR Interval Bins in Patients With and Without Arrhythmic Death Receiving Amiodarone or Placebo

Intervals/Ratio	$\overline{RR}$ bin	Amiodarone	Placebo	p Value*
QT				
550–560	Arrhythmic death†	334 ± 14	330 ± 14	0.259
	No arrhythmic death†	334 ± 17	327 ± 19	0.002
	p‡	0.474	0.305	
1140–1150	Arrhythmic death†	431 ± 23	452 ± 27	0.112
	No arrhythmic death†	476 ± 39	450 ± 40	2.3×10^{-8}
	p‡	0.005	0.455	
QTp				
550–560	Arrhythmic death†	255 ± 8	258 ± 17	0.337
	No arrhythmic death†	262 ± 17	261 ± 19	0.437
	p‡	0.181	0.273	
1140–1150	Arrhythmic death†	323 ± 19	367 ± 31	0.013
	No arrhythmic death†	374 ± 33	360 ± 32	0.0004
	p‡	0.0004	0.330	
TpTe				
550–560	Arrhythmic death†	79 ± 6	71 ± 3	0.126
	No arrhythmic death†	73 ± 2	66 ± 1	0.00005
	p‡	0.169	0.041	
1140–1150	Arrhythmic death†	108 ± 13	85 ± 5	0.003
	No arrhythmic death†	102 ± 17	89 ± 15	1.3×10^{-10}
	p‡	0.218	0.251	
TpTe/QT				
550–560	Arrhythmic death†	0.24 ± 0.04	0.22 ± 0.04	0.158
	No arrhythmic death†	0.22 ± 0.04	0.20 ± 0.03	0.001
	p‡	0.151	0.045	
1140–1150	Arrhythmic death†	0.25 ± 0.03	0.19 ± 0.02	0.001
	No arrhythmic death†	0.21 ± 0.03	0.20 ± 0.03	2.3×10^{-6}
	p‡	0.005	0.198	

*p Value refers to comparison between amiodarone group and placebo group.
†Mean ± SD.
‡p Value refers to comparison between patients with and without arrhythmic death.

TpTe prolongation with arrhythmic risk. Consistent with this finding, we did not observe any difference in TpTe between patients with and without arrhythmic death who received amiodarone. However, our finding of significantly longer TpTe intervals (at higher heart rates) in patients with arrhythmic death who received placebo suggests that under some circumstances this measure is related to arrhythmic risk. In other words, as is with QT interval, there might be both a "beneficial" and "bad" prolongation of the TpTe interval. Our findings might also possibly suggest that insofar as QTp and TpTe intervals are prolonged, amiodarone treatment is proportionally beneficial. However, when TpTe/QT is increased, arrhythmic risk is enhanced.

Because the TpTe interval is influenced by inaccuracies in both determination of the peak and the end of the T wave, its reliability might be questioned. However, in this study, automatic measurements were carefully visually validated to minimize this problem.

The analysis was performed on an intention-to-treat basis at randomization. It is likely that some of the patients receiving amiodarone discontinued the study medication during follow-up. However, because we found few differences in patients receiving placebo, the exclusion of patients who discontinued the study medication would only make our findings even more striking.

Despite the convincing in vitro concept and good accessibility of the TpTe interval as a measure of transmural repolarization heterogeneity, the inconsistencies addressed in this study suggest that extrapolation of results of experimental studies of myocardial tissue models to human surface electrocardiograms is problematic. More appropriate surrogates of the in vitro measured TpTe interval (e.g., the spatial morphology of the T wave) should be investigated.

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Syncope in Children and Adolescents and the Congenital Long QT Syndrome

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From a population-based epidemiologic cohort of children and adolescents who sought medical attention for syncope (n = 151), screening 12-lead electrocardiograms were obtained from 118 patients (79 female) to determine the frequency of significant QT prolongation. The distribution of heart rate corrected QT intervals (QTc) was compared with age- and sex-matched controls. Only one patient had QTc >470 ms. ©2003 by Excerpta Medica, Inc.

(Am J Cardiol 2003;92:746–749)

It is generally recommended that an electrocardiogram (ECG) be part of the current evaluation of syncope occurring in children and adolescents.[1,2] The prevalence of long QT syndrome (LQTS) in syncope is unknown. Before the molecular breakthroughs in LQTS, a QT interval corrected for heart rate (QTc), according to Bazett's formula, ≥440 ms was considered prolonged, and a QTc <420 ms was considered normal. However, more recent genotype–phenotype correlations have indicated that 25% to 40% of carriers of LQT1 and LQT2 mutations show QTc values (420 to 470 ms) that overlap with those of noncarriers.[3,4] In contrast, the prevalence of "fainters" having a nondiagnostic ECG with a QTc falling in this same range (420 to 470 ms) as patients with "incomplete penetrant" or "concealed" LQTS also is unknown. Such information is critical for proper interpretation of the screening ECG when evaluating a young person with syncope. Thus, the objectives of this study were to identify the frequency of significant and diagnostic QT prolongation (QTc >470 ms) as well as the frequency of a nondiagnostic ECG in a community-based population of fainters who sought medical attention compared with age- and sex-matched controls.

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Using data from the Rochester Epidemiology Project, 151 children and adolescents <21 years old, of whom 98 were female and 131 white, who lived in Rochester, Minnesota, were identified as having sought medical attention for an initial syncopal episode between 1987 and 1991.[5] The medical records of each patient were reviewed, and those without documentation of a screening ECG were contacted for participation in this Institutional Review Board-approved study. A 12-lead ECG was obtained from 118 (78%) patients (79 female) from this cohort. The QTc was computed both automatically using the Marquette MAC8 (GE Marquette Medical Systems, Inc., Milwaukee, Wisconsin) and manually. Manual determination of the QT interval was performed using guidelines similar to those reviewed by Moss.[6] One investigator (MWM) performed all manual QTc determinations using lead II and the standard Bazett's formula (QTc = QT/square root of RR interval). Diagnostically significant QT prolongation was defined as corrected QTc interval >470 ms.[7]

ECGs from 118 age- and sex-matched controls were obtained from Mayo Clinic's electrocardiography database. The age of controls was matched to the patient age at time of ECG rather than age at syncope,

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0002-9149/03/$–see front matter
doi:10.1016/S0002-9149(03)00846-4