Usefulness of Ventricular Repolarization Dynamicity in Predicting Arrhythmic Deaths in Patients With Ischemic Cardiomyopathy (from the European Myocardial Infarct Amiodarone Trial)

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The European Myocardial Infarct Amiodarone Trial (EMIAT) investigated the effects of amiodarone versus placebo in patients after myocardial infarction who had left ventricular ejection fraction ≤40% and were ≤75 years of age. The present substudy examined whether ventricular repolarization (VR) dynamicity could differentiate patients who died from cardiac death from their matched survivors in this EMIAT population. In addition, we assessed whether VR dynamicity could differentiate patients who died from arrhythmic cardiac death (ACD) and from non-ACD. VR dynamicity (determined from Holter's recordings at baseline) was compared before antiarrhythmic therapy in 118 patients who had cardiac death and 118 matched survivors according to age, gender, left ventricular ejection fraction, and subsequent administration or nonadministration of amiodarone. VR dynamicity was compared within the cardiac death group between the 59 patients who died from ACD and the 59 who died from non-ACD. VR dynamicity was expressed as the slope of the linear regression between QTo (measured automatically) and stable RR intervals. Patients who died were found to have a significant steeper rate dependence of QTo intervals during the 3 periods than their matched survivors. In multivariate analysis, the QTo/RR nocturnal interval appeared to be the best independent predictor of cardiac death. In addition, patients who died from ACD were found to have a significant steeper rate dependence of QTo intervals during the morning period than those who died from non-ACD. In the multivariate analysis, the QTo/RR morning interval remained the best independent predictor of ACD. Thus, in the EMIAT trial, evaluation of QT dynamicity is a strong predictor of cardiac death. In addition, QT dynamicity could predict the occurrence of ACD in cases of cardiac death. ©2005 by Excerpta Medica Inc.

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It is well established that ventricular repolarization (VR) abnormalities are associated with arrhythmic death after myocardial infarction (MI).[1,2] Using surface electrocardiography, noninvasive markers of VR such as QT or corrected QT intervals and QT dispersion have been assessed.[1–5] The QT interval corresponds to the time between the onset of depolarization and the end of repolarization of myocardial ventricular cells. Hence, the QT interval is usually considered the surrogate on the surface electrocardiogram of ventricular action potential. Despite its well-known limitations,[6,7] manual measurement of the QT interval on surface electrocardiography and its rate correction remain the usual quantitative evaluation of VR. The recent advent of digitized electrocardiography has encouraged multiple efforts to obtain alternative indexes. One of these new markers is the VR (or QT) dynamicity, which corresponds to the influence of heart rate and autonomic nervous system on the QT interval.[8,9] QT dynamicity, studied on 24-hour electrocardiographic recording, is 1 of the major characteristics of VR. This study assessed whether QT dynamicity could identify patients in the European Myocardial Infarct Amiodarone Trial (EMIAT) who had depressed left ventricular ejection fraction and those at high risk of cardiac death and arrhythmic cardiac death (ACD).

METHODS

Patient population: The study used the data of 24-hour ambulatory electrocardiographic monitoring (Holter) recorded at baseline ≤2 weeks after enrollment in the EMIAT study (before taking amiodarone or placebo therapy). The EMIAT[10] was a randomized, double-blind, placebo-controlled clinical trial designed to investigate whether amiodarone would decrease rates of all-cause mortality, cardiac mortality, and sudden cardiac death (considered to be ACD by the EMIAT validation committee) in patients who survived a recent MI. Among selected patients who had left ventricular ejection fractions ≤40% and were

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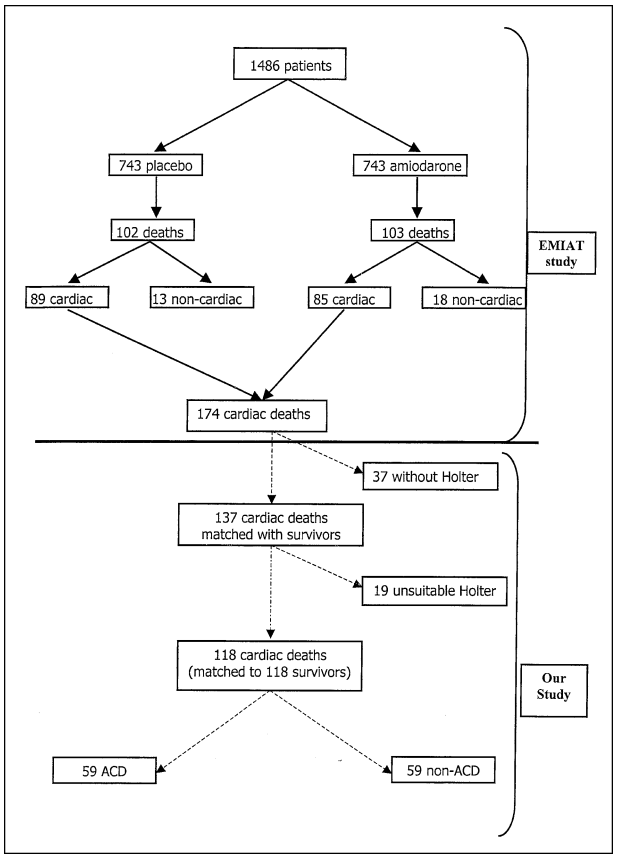

FIGURE 1. EMIAT population and remaining eligible patients for our substudy.

≤75 years of age, 1,486 were enrolled in the trial and followed for a mean duration of 21 months. Results showed no difference between treatment groups with regard to all-cause mortality and cardiac mortality, whereas a significant 35% decreased risk was observed in patients who developed ACD and had received amiodarone. The 83 cases of ACD and 91 cases of non-ACD in the EMIAT were used to assess QT dynamicity and QT duration in our substudy (Figure 1).

Holter's recordings: The 24-hour electrocardiograms recorded at baseline were centrally analyzed with a Marquette Laser Holter 8000 System (Marquette Medical Systems, Milwaukee, Wisconsin). The Holter's recording was considered suitable if it had no noise and contained >18 hours of recording and sinus rhythm. Tapes with average quality recording (noise), <18 hours of sinus rhythm, atrial fibrillation, and pacemaker-dependent cardiac rhythm were excluded. Each recording that fulfilled these criteria was subjected to evaluation for QT dynamicity and QT duration. All 24-hour electrocardiographic recordings with 2 bipolar electrocardiographic leads were reanalyzed and validated at 128 samples/s with detection and classification of identified QRS-T complexes. Electrocardiographic data and beat annotations were subsequently digitized for analysis of QT dynamicity and QT duration. Our methods of QT analysis from 24-hour electrocardiographic recordings has been previously reported.[11] Briefly, the major characteristic of this analysis was a selective beat averaging using QRS-T segments selected in a stable RR interval. Only QRS-T complexes that were preceded by a 1-minute period of heart rate stability (at 50, 60, 70 beats/min, and so forth) were extracted. To match stability criteria, the RR interval that preceded the target complex and the mean RR interval that was calculated over the preceding minute had to be identical (±15 ms). In addition, the 2 preceding RR intervals (RR-1 and RR-2) had to be similar to the RR interval that preceded the target complex (±25 ms). Selected complexes were subsequently averaged. Automatic measurements of the repolarization variable QTo (which corresponded to the interval between Q-wave onset and T-wave offset) was made. The method consisted of a filtered electrocardiogram to calculate the first and second derivatives to define the end of the T wave. T-wave offset was determined on the basis of first and second derivatives that matched specific, amplitude-independent conditions.

Three different circadian periods of analysis were defined according to subject diaries and average hourly heart rate. The first period consisted of the 8 consecutive diurnal hours with the fastest heart rate, the second consisted of the 4 consecutive sleeping hours with the lowest heart rate, and the third consisted of the 2 hours around the awakening heart rate acceleration. For each patient and for the 3 different periods, linear regression analysis between QTo intervals and corresponding RR intervals were performed. The slope of linear regression between QT and RR intervals was calculated to assess QT rate dependence. Establishing a stable heart rate during the preceding minute is required to obtain high correlation coefficients (>0.90), so that apparently small differences are significant. To avoid the questionable concept of corrected QT values, we prefer to speak of QT duration that is effectively measured from Holter's recordings. QTo duration was calculated at the actual cycle length of 1,000 ms (60 beats/min) or extrapolated when necessary by using the slope of linear regression between QTo and RR intervals for each different period.

Statistical analysis: All results are expressed as mean ± SD. Univariate analysis allowed screening of potential predictors of cardiac deaths. Student's *t* test was used for quantitative variables and chi-square or Fisher's exact test was used for qualitative or semiquantitative variables. Potential predictors (selected as $p < 0.1$ at univariate analysis) were then used to build a multivariate logistic model. Multivariate analysis was performed by conditional logistic regression analysis as proposed by Breslow and Day[12] using LogXact (Cytelsoftware, Cambridge, Massachusetts), a program that allows an exact method when necessary. Selection of independent predictors was made by a stepwise procedure. To assess the robustness of conclusions with regard to the importance of QT parameters, we also built an extended multivariate model where all potential clinical predictors were forced in the model and checked that, under these conditions,

TABLE 1 Results of Univariate Analysis of Clinical Characteristics, QT Dynamicity, and QTo 1,000 Parameters Along the Nycthemer of Cases of Cardiac Death and Control Patients

Variable	Alive (n = 118)	Cardiac Death (n = 118)	Univariate Analysis (p Value)
Age (yrs)	62 ± 9	63 ± 8	0.27
Men/women	97/21	97/21	1
Left ventricular ejection fraction (%)	27 ± 7	27 ± 7	0.78
New York Heart Association status (I/II–III)	40/78	44/74	0.59
Systolic blood pressure (mm Hg)	117 ± 18	118 ± 15	0.82
Diastolic blood pressure (mm Hg)	73 ± 10	72 ± 9	0.56
Mean heart rate (ms)	820 ± 134	775 ± 141	0.01
No. of ventricular premature complexes (24 hs)	754 ± 1,186	732 ± 1,330	0.89
β Blockers	35	38	0.67
QTo/RR diurnal interval	0.203 ± 0.07	0.247 ± 0.09	<0.0001
QTo/RR nocturnal interval	0.176 ± 0.06	0.229 ± 0.06	<0.0001
QTo/RR morning interval	0.225 ± 0.07	0.256 ± 0.08	0.037
QTo1,000 diurnal interval (ms)	452 ± 44	459 ± 45	0.22
QTo1,000 nocturnal interval (ms)	455 ± 48	460 ± 43	0.33
QTo1,000 morning interval (ms)	448 ± 81	456 ± 62	0.4

Values are mean ± SD.
QTo 1,000 = QTo interval at 1,000 ms.

TABLE 2 Results of Univariate Analysis of Clinical Characteristics, QT Dynamicity, and QTo 1,000 Parameters Along the Nycthemer of Cases of Arrhythmic and Nonarrhythmic Cardiac Death

	ACD (n = 59)	Non-ACD (n = 59)	Univariate Analysis (p Value)
Age (yrs)	62 ± 9	64 ± 7	0.17
Men/women	49/10	48/11	1
Left ventricular ejection fraction (%)	27 ± 7	27 ± 8	0.95
New York Heart Association status (I/II–III)	22/37	18/41	0.44
Systolic blood pressure (mm Hg)	115 ± 13	120 ± 16	0.07
Diastolic blood pressure (mm Hg)	72 ± 9	73 ± 9	0.56
Mean heart rate (ms)	770 ± 140	781 ± 144	0.65
No. of ventricular premature complexes (24 hs)	837 ± 1,459	596 ± 1,143	0.36
β Blockers	18	17	0.84
QTo/RR diurnal interval	0.255 ± 0.08	0.240 ± 0.08	0.36
QTo/RR nocturnal interval	0.237 ± 0.08	0.222 ± 0.07	0.22
QTo/RR morning interval	0.272 ± 0.07	0.239 ± 0.07	0.02
QTo 1,000 diurnal interval (ms)	459 ± 49	460 ± 41	0.94
QTo 1,000 nocturnal interval (ms)	462 ± 37	458 ± 37	0.64
QTo 1,000 morning interval (ms)	463 ± 44	448 ± 78	0.21

Values are mean ± SD. Abbreviation as in Table 1.

tests of QT parameters remained significant. We used this extended model to calculate the adjusted odds ratio for a given increase in QT parameters because the β coefficient of the variable in the logistic model provides the change in the log odds for an increase of 1 unit of the parameter. Because we identified a QT parameter as an independent predictor of death and because QT parameters can be highly correlated, we specifically studied, in a complementary analysis, the possible predictive values of other QT parameters when the QT parameter that had been identified as the best predictor was excluded from the model. In addition, to explore whether some QT parameters could predict type of death, univariate and multivariate analyses (nonstratified logistic regression) were performed for cases with type of death as the variable to be predicted. All tests were 2-sided with a 0.05 significance level.

RESULTS

Baseline characteristics: Among 174 patients, 37 died before undergoing the first Holter recording. Therefore, we were able to analyze 137 tapes (Figure 1). Therefore, the remaining 137 patients were matched with controls according to age, gender, left ventricular ejection fraction, and amiodarone or placebo therapy. Based on the need for high-quality recordings (that fulfilled suitable criteria) for analysis of QT dynamicity, 19 tapes (13%) were excluded but this exclusion did not influence the clinical characteristics of the study population. Therefore, the remaining 118 tapes were used for our QT analysis. No significant clinical and therapeutic (amiodarone therapy in 63 patients in each group, p = 1) differences were observed between cases of cardiac death and matched patients, except for mean heart rate, and in the subgroup analysis of cases of ACD and those of non-

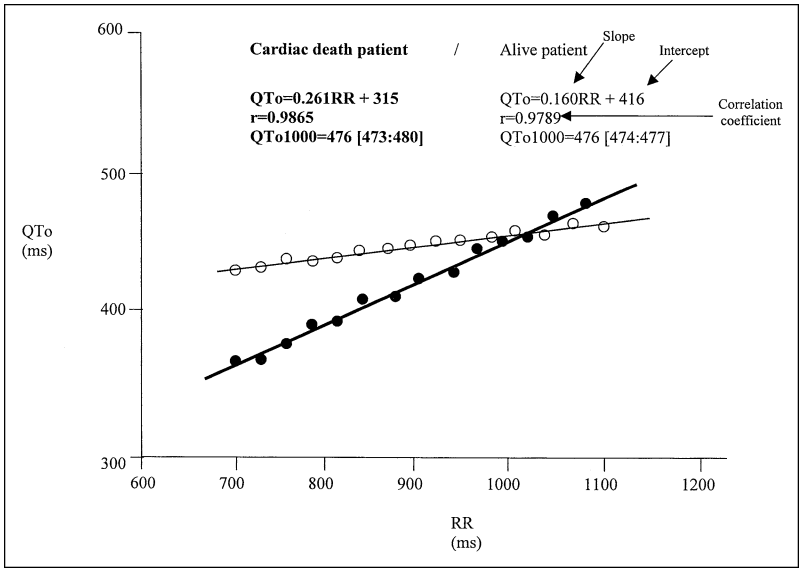

FIGURE 2. Comparison of nocturnal slopes between a case of cardiac death and a matched control patient. Slopes correspond to the linear regression between the QTo interval and the stable RR interval (QTo/RR). Steady-state analysis of QT dynamicity allowed a high coefficient of correlation (>0.90). QTo at 1,000 ms (QTo1000) is measured from the slope.

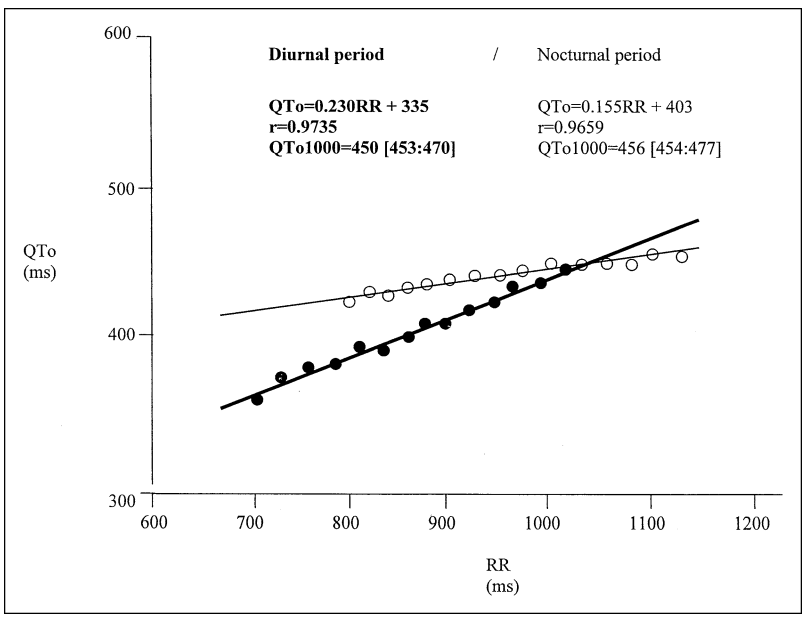

FIGURE 3. Comparison of diurnal and nocturnal slopes in a patient. Slopes correspond to the linear regression between the QTo interval and the stable RR interval (QTo/RR).

ACD. Clinical data of the overall (cardiac death vs alive) and subgroup (ACD vs non-ACD) analyses are presented in Tables 1 and 2.

VR dynamicity: QTo rate dependence: In the ACD group, a steeper rate dependence of the QTo interval than in the control group was observed within the 3 different circadian periods (Table 1). When analyzing type of cardiac death (ACD vs non-ACD), a steeper rate dependence of the QTo interval was observed in the ACD group during the morning period only, whereas QTo/RR diurnal and nocturnal slopes did not differ between ACD and non-ACD groups (Table 2). A schematic representation of a comparison of nocturnal slopes between a case of ACD and a control patient is depicted in Figure 2, and the circadian variation of QT rate dependence in a patient is shown in Figure 3.

QTo interval duration at 1,000 ms: The QTo interval at 1,000 ms did not discriminate patients who died from cardiac death and their controls (Table 1). When comparing ACD with non-ACD, the QTo interval at 1,000 ms similarly did not discriminate cases of ACD from cases of non-ACD (Table 2).

Multivariate predictors of cardiac death: Multivariate analysis showed that the QTo/RR nocturnal interval was the only independent predictor of cardiac death ($p < 0.001$). In the subgroup analysis, multivariate analysis showed that the QTo/RR morning interval was the only independent predictor of ACD among patients who died from cardiac death ($p < 0.02$). Other clinical parameters failed to reach statistical significance when building the multivariate logistic model in the 2 analyses. Robustness of these conclusions was tested by checking that these parameters (QTo/RR nocturnal interval for cardiac death and QTo/RR morning interval for ACD) was significant by the stepwise procedure for model building and when potential clinical predictors were forced in the model. An adjusted odds ratio that corresponded to an increase of 0.025 in the QTo/RR nocturnal interval was calculated from the multivariate model as equal to 1.42 (95% confidence interval 1.15 to 1.74) for cardiac death. Note that the other QT parameters were not independent predictors when the QTo/RR nocturnal interval was present in the model, but some parameters (QTo/RR diurnal interval and QTo/RR morning interval) reached statistical significance in alternative multivariate models from which the QTo/RR nocturnal interval was excluded. For ACD, an adjusted odds ratio that corresponded to an increase of 0.025 in the QTo/RR morning interval was calculated from the multivariate model as equal to 1.15 (95% confidence interval 1.01 to 1.31). Note that the other QT parameters were not independent predictors when the QTo/RR morning interval was present in the model.

DISCUSSION

In this subanalysis of basal 24-hour electrocardiographic recordings (before taking amiodarone or placebo therapy) of the EMIAT, we found that QT dynamicity could discriminate patients who died from cardiac death from survivors after recent MI with decreased left ventricular ejection fraction. Further, we were able to predict type of cardiac death (ACD vs non-ACD). This is the first study in which a noninvasive marker was powerful and reliable enough to predict cardiac death and specific ACD.

Corrected QT duration is used to compare static values of QT in a population, whereas QT dynamicity is used to assess QT changes in patients. Using a formula to evaluate QT modulation seems meaningless because no rate formula will ever compensate for circadian QT changes assessed at identical RR intervals. A formula that is supposed to correct for rate would be useless, and Malik et al[13] showed that any rate correction should be different for every patient, as a consequence, a corrected formula would be useless.

From experimental data, it is well established that abnormal VR contributes to cardiac electrical instability.[1–5] On surface electrocardiography, Schwartz et al[1] reported a predictive value for sudden cardiac death of the corrected QT interval after an MI. Algra et al[2] showed that corrected QT duration by Bazett's formulas correlated with mortality (by sudden cardiac death) after MI only when left ventricular ejection fraction is preserved. Conversely, Extramiana et al[14] and Yi et al[15] found no such predictive value of corrected QT duration in their patients after MI. In our study, the 1,000-ms QTo interval did not differ between cases of cardiac death and controls when comparing the mechanism of cardiac death (ACD vs non-ACD). From the example shown in Figure 2, it is clear that a QTo interval at 1,000 ms generally cannot differentiate dead from live patients because of a crossing point between slopes at a cycle length near 1,000 ms. Hence, QT duration has produced controversial results for prediction of cardiac and arrhythmic deaths in patients after MI, and we believe it should not be considered a reliable noninvasive index.

Several studies have assessed QT dynamicity as a marker of mortality in different pathologic situations.[14,16–18] In congenital long-QT syndrome, Neyroud et al[17] reported a steeper rate dependence of nocturnal QT interval. Kluge et al[18] reported an increased QT rate dependence in patients who had MI with ventricular arrhythmias than in those who had MI without ventricular arrhythmias. In a retrospective study, Extramiana et al,[14] found that patients who had MI with ventricular arrhythmias had a steeper QT rate dependence than did patients who had MI without ventricular arrhythmias regardless of the circadian period considered. Our results concur with these findings and provide additional information with identification of specific ACD using QT rate dependence.

Clinical implications in diseased myocardium: Among various factors of variation in QT duration, heart rate and the autonomic nervous system appeared to be the most influential factors.[8,9] Evaluation of QT rate dependence on Holter's recording provides a closed pattern to assess the influence of autonomic nervous system independently of heart rate when studying QT duration separately in different periods of the nycthemer. Several studies have reported a steeper rate dependence of the QT interval in patients at high risk of death after a MI or in the setting of long-QT syndrome.[14,16–18] Hence, a common characteristic of diseased myocardium is the existence of a steeper QTo/RR slope. This finding may suggest an impaired balance of the autonomic nervous system, such as enhanced sympathetic activity or decreased vagal tone in diseased hearts, particularly during the nocturnal period (with presumably increased sympathetic tone),[19,20] and QTo/RR interval relations could be a marker of such phenomenon. Therefore, it was not surprising to find that the nocturnal QTo/RR interval was the strongest independent predictor factor of cardiac death in multivariate analysis. Previous reports have emphasized a circadian variation in the frequency of MI and death,[21,22] with an abnormally high incidence of sudden cardiac death during the awakening period. In this subgroup analysis, the steepest slope of QTo/RR morning interval was found in patients in whom ACD was the mechanism of cardiac death. Further, in the multivariate analysis, morning slope appeared to be an independent predictor of ACD. This finding suggests that the QTo/RR morning interval may be a marker of patients at high risk of ACD. This observation of the steepest slope occurring while awakening could serve as a pathophysiologic explanation for sudden cardiac death after MI, with a short RR cycle indicating a shorter action potential duration that could lead to reentry phenomenon and a long RR cycle indicating a longer action potential duration that could lead to Torsades de pointes. Hence, studying the relation between the QT interval and stable RR intervals may contribute to a better understanding of a likely initiation of fatal ventricular arrhythmias. Our results suggest that, in clinical practice, spotting patients who have an abnormal QT dynamicity, particularly during the morning, could help to identify those at high risk of ACD for whom efficient therapy is available.

QT dynamicity evaluation requires a suitable 24-hour electrocardiographic recording to provide accurate automatic measurements of the QT interval and relevant calculation of a linear regression between QT and RR intervals. According to this criterion, 19 patients were excluded because of an unsuitable recording. As a consequence, despite improving the quality of recording, this new noninvasive approach may have limitations for assessing VR dynamicity as a marker of death. The definition of ACD in the EMIAT involves sudden and nonsudden cardiac deaths. In sudden cardiac death, the ratio of documented arrhythmic death appears to be less important than death that is presumed to be arrhythmic. Thus, an electromechanical dissociation that occurred <1 hour after new symptoms may have been considered and presumed to be arrhythmic. As a result, the number of patients in this group may have been an overestimate.

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