

Original Article

Accuracy of Electrocardiography Indices for Prediction of Life Threatening Ventricular Arrhythmias after Acute Myocardial Infarction

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Kuwait Medical Journal 2007, 39 (1): 19-25

ABSTRACT

Objectives: The hypothesis of this study was that the absence HRT is a valid and reliable independent method for detecting life threatening arrhythmias (LTA) in patients.

Design: Prospective cohort study conducted between January 2000 and April 2004.

Setting: Coronary Care Unit, Department of Medicine, Farwania Hospital, Kuwait.

Subjects: One hundred and forty patients with AMI and VPCs were included.

Intervention: Echocardiography was done to exclude patients with left ventricular (LV) systolic dysfunction and mechanical complications.

Main outcome Measures: Electrocardiograph (ECG) was done to analyse the HRT after VPCs and QT dispersion. There were two groups; Group I: included 60 patients with LTA and Group II: included 80 patients without

LTA.

Results: Stepwise logistic analysis revealed that there was no significant relation between age, gender, left ventricular diastolic dysfunction, frequent VPCs, ventricular couplets and non-sustained ventricular tachycardia and the LTA in patients with AMI ($p = NS$) but there was a significant relation between the absence of HRT and presence of QT dispersion and the LTA after AMI ($p < 0.05$). Predictive indices of HRT and QT dispersion for prediction of LTA revealed that the sensitivity (75% versus 63%), specificity (75% versus 65%), accuracy (76% versus 64%), positive predictive value (42% versus 43%) and negative predictive value were 58% versus 57% respectively.

Conclusion: Absence of the heart rate turbulence after ventricular premature beats is an independent predictor of life threatening ventricular arrhythmias after AMI.

KEY WORDS: heart rate turbulence, sustained ventricular tachycardia, ventricular fibrillation

INTRODUCTION

Recently, a new electrocardiographic phenomenon termed heart rate turbulence (HRT) has been described^[1]. Clinical trials suggest that in high-risk patients with ischemic heart disease, mortality can be effectively reduced by implantation of a cardioverter-defibrillator^[2]. Since the selection of high-risk patients is a crucial part of prophylaxis, risk stratification strategies are important. In patients surviving AMI, predictive value of currently used risk factors, such as left ventricular dysfunction, frequent ventricular ectopics, non-sustained ventricular tachycardia, positive late potentials, heart rate variability and mean heart rate is modest even when several predictors are combined^[3]. Schmidt *et al*, described a new method for risk stratification based on a simple expression of ventriculophasic sinus arrhythmia, namely fluctuations of sinus-rhythm cycle length after a single VPC^[4]. In low-risk patients, they observed that after a VPC, sinus rhythm shows a characteristic

pattern of early acceleration and subsequent deceleration. They termed such fluctuations heart rate turbulence (HRT). Such a characteristic pattern does not occur in high-risk patients. The pathophysiologic correlates of HRT remain speculative and are believed to rise from the hemodynamic changes and baroreceptor reflexes that occur following a VPC^[5,6].

The aim of this study was to evaluate the usefulness of the impaired heart rate turbulence and QT dispersion in prediction of the LTA in patients with AMI.

PATIENTS AND METHODS**Study patients:**

One hundred and forty patients (130 men and 10 women) with AMI and VPCs were included in the study. Their ages ranged between 49 and 63 years with a mean of 57 ± 3.12 years. All patients were admitted by their physicians to the Coronary Care Unit, Department of Internal Medicine,

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Farwania Hospital with a clinical diagnosis of AMI between January 2000 and April 2004. Arrival time (time from onset of chest pain to arrival at the hospital) of patients was between 30 to 80 minutes with a mean of 50 minutes. Twenty two (15%) patients had anterior MI, 28 (21%) had anteroseptal MI, 37 (26%) had extensive anterior MI, 30 (22%) had inferior MI and 23 (16%) had posterior MI. All patients had ST segment elevation MI. The mean time of discharge from the hospital was five days.

Exclusion criteria included patients with complicated AMI like those with rupture papillary muscle, perforated ventricular septum, rupture free wall of the left ventricle, cardiac tamponade, atrio-ventricular conduction defects, cardiogenic shock and severe left ventricular failure with acute pulmonary edema.

Exclusion was based on medical history, physical examination, routine biological, chemical tests, and echocardiography.

Life threatening arrhythmias (LTA) are defined as arrhythmias associated with hemodynamic compromise in cases of sustained ventricular tachycardia and ventricular fibrillation⁹.

Data collection:

Clinical and electrocardiographic characteristics were collected prospectively. Forty-six patients developed sustained ventricular tachycardia (10 patients on the first day of admission, 18 patients on the second day, five patients on the third day, 13 patients on the fourth day of admission) and 14 patients developed ventricular fibrillation (four patients on the first day, two patients on the second day, five patients on the third day and three patients on the fourth day of admission).

There were two groups:

Group I: included 60 patients with LTA (46 patients developed sustained ventricular tachycardia and 14 patients developed ventricular fibrillation).

Group II: included 80 patients with VPCs but without LTA.

Measurement of the QT dispersion:

The QT interval was measured manually by two observers using calipers from the onset of the QRS to the end of the T wave defined as the return to the TP baseline. When U waves were present the QT interval was measured to the nadir of the curve between the T and U waves. Three consecutive cycles were measured in each of the standard 12 leads and from the three values a mean QT interval was calculated. When the end of the T wave could not be identified the lead was not included. A minimum of seven leads (including at least three precordial leads) were required for QT dispersion to be calculated. The QT dispersion (QTd) was

defined as the difference between the maximum and minimum QT interval occurring in any of the 12 ECG leads. Heart rate correction of the measured QT dispersion was done using Bazett's formula and corrected QTd was calculated by measuring the difference between maximum and minimum corrected QT intervals in each ECG tracing¹⁷.

Ventricular premature complexes (VPCs):

Coupling interval is an interval between the R wave of VPC and R wave of the preceding sinus QRS complex. Compensatory pause is an interval between the R wave of VPC and R wave of the following sinus QRS complex.

Heart rate turbulence analysis:

One factor was selected to characterize the chronotropic response of sinus rhythm to VPCs. The immediate initial acceleration was quantified by the relative change of RR intervals immediately after compared with immediately before a VPC and was termed the turbulence onset. HRT onset is defined as the difference between the mean of the first two sinus RR intervals after a VPC and the last two sinus RR intervals before the VPC divided by the mean of the last two sinus RR intervals before the VPC. In other words: "HRT onset = $(RR1 + RR2) - (RR2 + RR1) / (RR2 + RR1)$ ".

For instance, in one patient, the coupling interval of the ectopic is preceded by RR intervals of 820 ms and 828 ms and its compensatory pause is followed by RR intervals of 680 ms and 668 ms. Thus, in this case, HRT onset = $(680 + 668) - (820 + 828) / (820 + 828) = -0.18\%$.

These measurements were first performed for each individual singular VPC and then averaged to obtain the value characterizing the patient. Positive values of HRT onset mean sinus rhythm deceleration after a VPC and negative turbulence onset means sinus rhythm acceleration after a VPC¹⁸.

Echocardiographic study:

Echocardiography was performed for all patients in the study with the use of Toshiba (Power Vision) and GE Vivid 7 with a 3.5 MHZ phased array transducer. All echocardiographic studies were performed by the same cardiologist. Pulsed Doppler echocardiography was obtained from the standard apical four chamber view. Mitral inflow velocity was recorded with the sample volume at the mitral annulus level. The transducer was then manipulated to obtain the maximal flow velocity as assessed by the auditory and spectral outputs. The Doppler measurements were made over at least three cardiac cycles using the darkest part of the spectral recording and were averaged. The following measurements were obtained, viz, peak

Table 1: RR interval before and after PVC, coupling interval and compensatory pause in both groups of the study

	Group I	Group II	p-value
RR-interval before PVC (ms)	862 ± 80	791 ± 92	NS
RR-interval after PVC (ms)	611 ± 78	780 ± 86	< 0.05
Coupling interval (ms)	408 ± 30	465 ± 42	NS
Compensatory pause (ms)	1100 ± 102	982 ± 81	NS

ms = millisecond, PVC = premature ventricular complex

Table 2: Multivariate logistic analysis of the patients with LTA versus those without LTA as regards different variables

Variables	Coefficient	95%CI	p-value
Absence of HRT	0.5873	1.761 - 3.793	<0.05
QT dispersion	0.6321	1.629 - 2.095	<0.05
Frequent PVCs	0.1361	0.369 - 1.026	NS
Ventricular couplets	0.2091	0.125 - 1.091	NS
NSVT	0.0813	0.703 - 1.503	NS

LTA = life threatening arrhythmias, CI = confidence interval, HRT = heart rate turbulence, NSVT = non-sustained ventricular tachycardia, PVC = premature ventricular complex

velocity of early left ventricle filling (E), peak velocity of late left ventricular filling (A) and the ratio between early and late flow velocity (E/A).

Statistical analysis:

Continuous variables are summarized as a mean ± standard deviation (SD). Comparison between two groups was performed with t-test for continuous variables and Chi-square test for categorical variables. A p-value < 0.05 was considered statistically significant and a p-value < 0.01 was considered statistically highly significant. A stepwise multivariate regression model was used to identify possible independent variables associated with LTA in the patients with AMI. The strength of the association with LTA is presented as 95% confidence intervals. Potential confounding of clinical variables were entered as independent variables.

The validity of the absence of HRT and QT dispersion to detect LTA after AMI was assessed by estimating the predictive indices and Kappa coefficient to determine overall agreement with the data obtained from the bed-side ECG monitoring and 12-lead ECG documented ventricular arrhythmias.

Kappa coefficient value (K) = (Observed frequency of agreement - Expected frequency of agreement) / (Total observed - Expected frequency of agreement).

Predictive indices:

True positive (TP), true negative (TN), false positive (FP) and false negative (FN) values were calculated. Sensitivity = TP / (TP+FN), Specificity = TN / (TN+FP), Positive Predictive Value = TP /

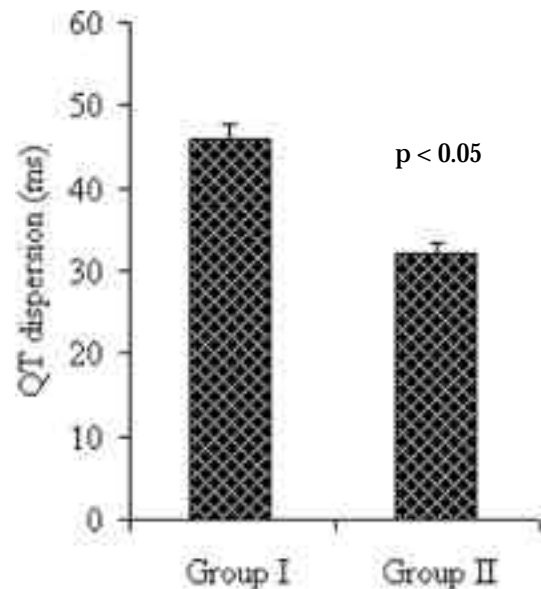


Fig. 1: Qt dispersion in the patients of both groups of the study

(TP+TN), Negative Predictive Value = TN / (TN+TP) and Accuracy = (TP+TN) / (TP+TN+FP+FN) were also calculated.

RESULTS

Clinical characteristics:

There was no significant difference (p = NS) between patients in the two groups of the study as regards their age, gender, diabetes mellitus status (type 1 and type 2), hypertension, smoking status, number of the patients with history of therapy with beta-blockers, nitrates, calcium channel blockers, acetyl salicylic acid, number of the patients with history of previous MI, post-MI angina, arrival time to the hospital, time to give thrombolytic therapy, site of MI (anterior, anteroseptal, extensive anterior, inferior and posterior MI).

Intergroup difference:

There was no significant difference (p = NS) between both groups as regards their laboratory investigations (serum sodium, serum potassium, blood sugar, renal and liver function tests). Also there was no significant difference (p = NS) between both groups as regards ventricular premature complexes in the form of ventricular couplets, ventricular bigeminy, non-sustained VT and R on T phenomenon. There was no significant difference (p = NS) between the patients of both groups as regards the RR-interval before VPC, coupling interval and compensatory pause but there was a significant decrease in the RR-interval after VPC in patients who had LTA as compared with the patients in Group II (p < 0.05, Table 1).

As regards QT dispersion, there was a significant increase in QT dispersion in those

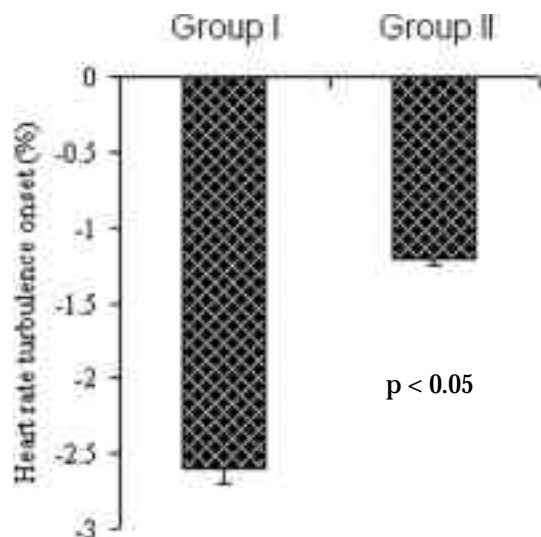


Fig. 2: Heart rate turbulence onset in the patients of both groups of the study

patients who had LTA than those in Group II (46 ± 5.4 ms versus 32 ± 6.3 ms, $p < 0.05$, Fig. 1).

There was a significant decreased-HRT in patients from Group I than those of Group II (-2.5% versus -1.2% , $p < 0.05$, Fig. 2).

Echocardiography:

There was no significant difference ($p = \text{NS}$) between patients of both groups as regards the left ventricular systolic and diastolic function and site of the segmental wall motion abnormalities. No patients with mechanical complications (rupture of papillary muscle, rupture of ventricular septum, rupture of free wall of left ventricle or cardiac tamponade) were included in the study. All patients had normal aortic root with no signs of aortic root dissection. No patient had right ventricular dilatation or tricuspid regurge.

Multivariate analysis:

Stepwise logistic analysis revealed no significant relation between age, gender, serum potassium, diabetes mellitus status, left ventricular diastolic dysfunction, frequent VPCs, ventricular couplets and non-sustained ventricular tachycardia and the LTA in patients with AMI ($p = \text{NS}$).

Stepwise logistic analysis revealed no significant relation ($p = \text{NS}$) between frequent VPCs, ventricular couplets and non-sustained ventricular tachycardia and the LTA in patients with AMI but there was a significant relation ($p < 0.05$) between the absence of HRT and presence of QT dispersion and the LTA after AMI (Table 2).

Agreement and predictive indices:

There was good agreement between data of LTA and both HRT and QT dispersion as shown by the Kappa coefficient (0.824 for HRT versus 0.672 for

Table 3: Agreement of the ECG documented LTA and ECG-based HRT onset after ventricular premature beats

	LTA +ve	LTA -ve	Total
Absence of HRT	45	18	63
Intact HRT	15	62	77
Total	60	80	140

Kappa Coefficient value (k) = 0.824

HRT = heart rate turbulence, LTA = life threatening ventricular arrhythmias

Table 4: Agreement of the ECG documented LTA and the 12-lead ECG -based QT dispersion

	LTA +ve	LTA -ve	Total
QT dispersion +ve	38	28	66
QT dispersion -ve	22	52	74
Total	60	80	140

Kappa Coefficient value (k) = 0.672

LTA = life threatening ventricular arrhythmias

QT dispersion, Table 3 and 4).

The predictive indices showed that HRT assessment is more valid than QT dispersion for prediction of patients with LTA as its sensitivity was 75% versus 63%, specificity 78% versus 65%, accuracy 76% versus 64%, positive predictive value 42% versus 43% and negative predictive value 58% versus 57%, respectively. It also had a lower number of false positive (18 versus 28, respectively) and false negative (15 versus 22, respectively) results as regards the HRT analysis when compared with results of QT dispersion (Table 5).

Reproducibility:

There was no significant difference in inter-observer variability and intra-observer variability as regards HRT analysis and QT dispersion ($p = \text{NS}$, Tables 6 and 7).

Receiver operating characteristic (ROC) curve of QT dispersion and HRT revealed that 100% sensitivity has a probability of error of 34% versus 30% respectively (Figs. 3 and 4).

DISCUSSION

Almost a century after Einthoven's invention of the string galvanometer, the surface ECG retains its central place in cardiological diagnosis. In seeking to extract yet more information from the standard 12 lead ECG, much attention has been given in recent years to the measurement of QT dispersion^{9,10}. Other electrocardiographic predictors are heart rate variability, late potentials, ST-T changes and prolonged QT interval¹¹.

The exact mechanism of HRT is not known. However, it is thought that HRT reflects the baroreflex response¹¹. When a VPC appears early in the cardiac cycle, subsequent stroke volume is

Table 5: Indices for prediction of LTA by HRT and QT dispersion after AMI

	TP	TN	FP	FN	Sen	Spec	Acc	PPV	NPV
Absent HRT	45	62	18	15	75%	78%	76%	42%	58%
QT dispersion	38	52	28	22	63%	65%	64%	43%	57%
HRT and QTd	38	52	18	15	72%	74%	73%	42%	57%

LTA = life threatening arrhythmias, HRT = heart rate turbulence, AMI = acute myocardial infarction, TP = true positive, TN = true negative, FN = false negative, FP = false positive, Sen = sensitivity, Spec = specificity, Acc = accuracy, PPV = positive predictive value, NPV = negative predictive value, HRT = heart rate turbulence, QTd = QT dispersion

Table 6: Intra-observer and inter-observer variability in measurement of QT dispersion in the patients with AMI

	Intra-observer variability (1)	Intra-observer variability (2)	Inter-observer Variability
Absolute difference	6 ms	5 ms	4 ms
p - value	NS	NS	NS

NS = not significant

Table 7: Intra-observer and inter-observer variability in measurement of heart rate turbulence onset after VPC's

	Intra-observer variability (1)	Intra-observer variability (2)	Inter-observer Variability
Absolute difference	0.51%	0.49%	0.41%
p - value	NS	NS	NS

NS = not significant

reduced and there is a reduction in cardiac output^[12]. Consequently, there is a shortening of the RR interval to compensate for the reduced stroke volume^[13]. This is initially brought about by vagal withdrawal, a reflex with shorter latency and faster reaction time than sympathetic nervous system activation^[14]. Conversely, following the VPC and compensatory pause, there is an increase in stroke volume and blood pressure for the normal sinus beat following the VPC^[15]. The compensatory increase in vagal tone causes RR intervals to lengthen^[1].

Univariate and multivariate analysis in this study revealed that QT dispersion and HRT were independent predictors of LTA after acute myocardial infarction but the predictive indices of HRT were better than QT dispersion. The receiver operating characteristic curve showed that HRT had less probability of false positive results (1-specificity) than QT dispersion.

Ghuran *et al*^[16] from St. George's Hospital Medical School, reported that their multivariate analysis revealed that HRT slope and the combination of abnormal HRT onset and slope remained significant, adding independent prognostic information to that obtained from other established risk predictors, such as baroreflex sensitivity, heart

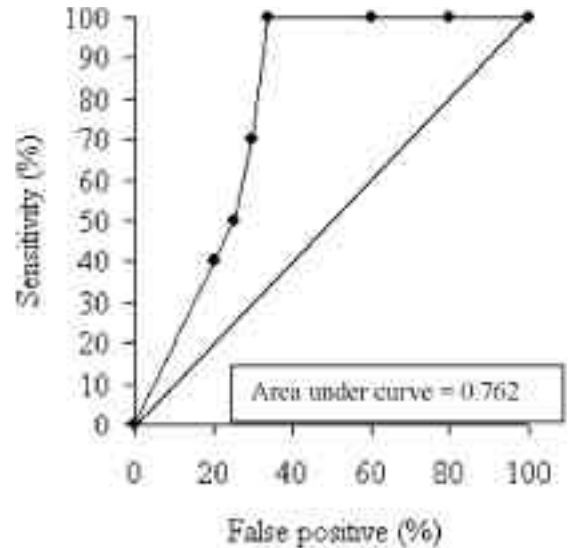


Fig. 3: Receiver operating characteristic (ROC) curve of QT dispersion : 100% sensitivity has 34% probability of error

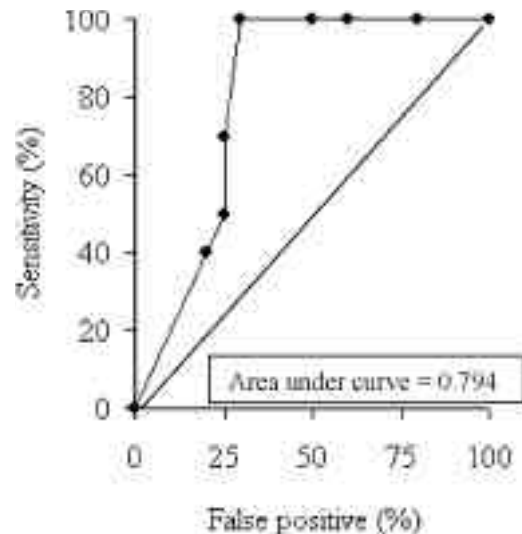


Fig. 4: Receiver operating characteristic (ROC) curve of HR turbulence: 100% sensitivity has 30% probability of error

rate variability, left ventricular ejection fraction, VPCs / hour and the age.

Heart rate variability partly reflects sympathovagal modulation. Holter based heart rate variability is assessed over 24 hour and is therefore, affected by a broad variety of physiologic factors including autonomic, thermoregulatory, emotional and environmental influences^[17]. Therefore, it is believed that the physiology of HRT, which represents an almost instantaneous response to a VPC, is also different from the long-term measure of heart rate variability. This again is reflected by the graphic distribution and modest correlation between heart rate variability and HRT. Although HRT, baroreflex sensitivity and heart rate variability all reflect autonomic function, each indexes different facets of autonomic regulation. Consequently, by combining HRT, baroreflex sensitivity and heart rate variability, a multivariate assessment of cardiac autonomic

status can be determined. Indeed, a composite autonomic index provided excellent prediction of fatal cardiac arrest and non-fatal cardiac arrest^[18].

The measures for quantifying HRT were developed in one population of the patients with ischemic heart disease and prospectively tested with masking in two large and independent populations taken from multicentre post-infarction trials, the Multicentre Post-Infarction Program (MPIP) and European Myocardial Infarction Amiodarone Trail (EMIAT). Because of the treatment practice changes, more patients in EMIAT than in MPIP received thrombolysis, β -blockers and inhibitors of angiotensin-converting enzyme (ACE). These differences show that our finding is independent of modern management of post-infarction patients. The MPIP population was also an unselected population of post-infarction patients, whereas only patients with low left ventricular ejection fraction were enrolled in the EMIAT trial^[19].

HRT is a predictor of mortality containing information additional to other established risk factors^[20,21]. The combination of turbulence onset and slope was a very strong risk predictor in patients of the MPIP trial and of the placebo group of EMIAT, even when adjusted for other established mortality predictors, such as left ventricular ejection fraction, arrhythmia count, heart rate variability, mean heart rate and history of previous myocardial infarction. HRT onset and slope in combination was by far the strongest Holter-based risk predictor.

It has long been known that ventricular systole can influence the rate of sinus nodal discharge, even in the absence of retrograde atrioventricular conduction. As early as 1909, first observations of the so-called ventriculophasic sinus arrhythmia were made in experimental atrioventricular block^[22,23].

Various pathophysiological mechanisms have been discussed to explain the ventriculophasic mechanisms, including changes in autonomic tone, traction on the atrium as well as atrial appendages, atrioventricular junction and the sinus nodal region and transient improvement of the blood supply to the sinus node^[24,25].

Compared to other non-invasive risk predictors, the relative risk and positive predictive accuracy of HRT are only modestly better, but the ease with which it can be measured and its applicability as a predictor in patients on beta-blockers makes HRT significantly more attractive. One might even instruct general practitioners to see any change in RR interval after a random VPC on an electrocardiogram at least 12 ms from the shortest to the longest RR within 10 beats after VPC^[1].

The confounding factors:

Coupling interval and the ambient heart rate may influence the phenomenon of HRT and may seriously confound the results^[26,27]. The reperfusion injury after the thrombolytic therapy in successful revascularization or the failure of the thrombolytic therapy with persistent myocardial ischemia may also confound the results^[28].

Limitations of the study:

1. Only one center experience
2. The study is not completely blind to the observers.
3. HRT is impossible to assess in patients with atrial fibrillation and when the patients do not have any VPCs.
4. Signal average ECG was not included in the design of the study.
5. Holter monitor is more accurate for analysis of HRT parameters including novel HRT measures, HRT frequency, HRT timing, HRT slope and HRT jump^[1].
6. Assessing cardiac autonomic function, created by combining HRT and 24-hour HR variability may be a stronger predictor of the life threatening ventricular arrhythmias^[11,16].

CONCLUSION

HRT is a simple and elegant way of measuring cardiac autonomic function in patients at risk. Despite the limitations and the confounders of our approach, this study confirms the independent value of the absence of the characteristic heart-rate patterns after VPCs in predicting LTA after AMI.

ACKNOWLEDGMENTS

The authors honor and thank Dr Saleh Ali Al-Enezi, Chairman, Department of Medicine, Dr Ahmed Al-Dousari, Consultant Endocrinologist and Dr Samuel Cherian and all other colleagues of the Medicine Department of Farwaniya Hospital for their valuable support and contributions to make this study successful. We are also indebted to Dr Mousa Akbar, Consultant Cardiologist of Sabah Hospital for his valuable assistance and timely advice.

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