The ventricular ectopic QRS interval (VEQSI):

A potential marker for ventricular arrhythmia in ischaemic heart disease

Rachel Bastiaenen PhD[1,2], Hanney Gonna MRCP[1,2,3], Navin Chandra MD[2],

Ahmed Merghani MRCP[2], Oswaldo Valencia MD[1],

A. John Camm MD*[1,2] and Mark M. Gallagher MD*[1,2].

[1]Department of Cardiology, St George's University Hospitals NHS Foundation Trust, London, UK

[2]Institute of Cardiovascular and Cell Sciences, St George's University of London, UK

[3]National Heart and Lung Institute, Imperial College London, UK

* The authors indicated contributed equally to the work

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Corresponding Author

Dr Mark M. Gallagher, Director of Cardiac Electrophysiology, St George's Hospital NHS Foundation Trust, London SW17 0QT, United Kingdom

Email mark_m_gallagher@hotmail.com Tel 02087253079 Fax 02087254117

ABSTRACT

Background

The ventricular ectopic QRS interval (VEQSI) has been shown to identify structural heart disease and predict mortality in an unselected population. In ischaemic heart disease (IHD), risk stratification for sudden death is imperfect. We hypothesized that VEQSI would identify patients with prior myocardial infarction (MI) compared with healthy subjects and distinguish IHD patients who have suffered life threatening events from those without prior significant ventricular arrhythmia.

Methods

12-lead Holter recordings from 189 patients with previous MI were analysed: 38 with prior life threatening events (MI-VT/VF; 66±9years; 92% male); 151 without prior significant ventricular arrhythmia (MI-no VT/VF; 64±11years; 74% male). These were compared with 60 normal controls (62±7 years; 70% male). All ventricular ectopic beats (VEB) were reviewed and VEQSI max was recorded as the duration of the longest VEB.

Results

VEQSI max was longer in post-MI patients compared with normal controls (185±26ms vs 164±16ms; $p<0.001$) and in MI-VT/VF patients with prior life threatening events compared with MI-no VT/VF patients without prior life threatening events (214±20ms vs 177±22ms; $p<0.001$). Multivariate analysis established VEQSI max as the strongest independent marker for prior serious ventricular arrhythmia. VEQSI max >198ms had 86% sensitivity, 85% specificity, 62% positive predictive value and 96% negative

predictive value for identifying patients with prior life threatening events (Odds Ratio 37.4; 95% CI 13.0-107.5).

Conclusions

VEQSI max >198ms distinguishes post-MI patients with prior life threatening events from those without prior significant ventricular arrhythmia. This may be a useful additional index for risk stratification in IHD.

Keywords

IHD, ischaemic heart disease; ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death; VEQSI, ventricular ectopic QRS interval; VEB, ventricular ectopic beat

CONDENSED ABSTRACT

We examined the maximal ventricular ectopic QRS interval (VEQSI) duration during 12-lead Holter monitoring in 60 normal controls and 189 patients with previous myocardial infarction (MI): 38 with prior life threatening events (MI-VT/VF); and 151 without prior events (MI no-VT/VF). VEQSI max was longer in post-MI patients compared with controls and in MI-VT/VF patients compared with MI-no VT/VF patients. Multivariate analysis established VEQSI max as the strongest independent marker for prior life threatening events. VEQSI max >198ms distinguished MI-VT/VF patients from MI-no VT/VF patients with 86% sensitivity and 85% specificity. This may represent an additional index for post-MI risk stratification.

ABBREVIATIONS

LVEF = left ventricular ejection fraction

SCD = sudden cardiac death

ICD = implantable cardioverter-defibrillator

IHD = ischaemic heart disease

MI = myocardial infarction

VEB = ventricular ectopic beat

VEQSI = ventricular ectopic QRS interval

MI-VT/VF = prior myocardial infarction and life threatening ventricular arrhythmia

MI-no VT/VF = prior myocardial infarction and no significant ventricular arrhythmia

ECG = electrocardiogram

NSVT = non-sustained ventricular tachycardia

VF = ventricular fibrillation

INTRODUCTION

In patients with ischaemic heart disease (IHD), reduced left ventricular ejection fraction (LVEF) remains the best established predictor of sudden cardiac death (SCD).(1–3) However, in primary prevention trials which selected individuals for implantable-cardioverter defibrillator (ICD) therapy predominantly on the basis of reduced LVEF, only one third had appropriate device therapy over the 3-5 year follow-up.(1; 2) This raises concern that many patients are exposed to the risk and expense of ICD therapy from which they receive no benefit. The converse is of greater concern: as most IHD-related SCD occurs in patients with LVEF >35%, many who might benefit are denied the protection of an ICD if this criterion is used alone.(4)

Of many electrocardiographic indices proposed as markers of risk for SCD, only the conducted QRS interval has shown consistent predictive value in survivors of myocardial infarction (MI).(1) With an intact conduction system, however, the QRS remains narrow even in the presence of ventricular dilatation and impairment. Ventricular ectopic beats (VEB) are usually conducted through ventricular myocardium with limited participation of specialized conduction tissue and should therefore provide a better index of the state of the myocardium and risk of SCD.(5) In an unselected population attending for Holter monitoring, we have shown that the ventricular ectopic QRS interval (VEQSI) and number of VEB morphologies correlated with the presence of structural heart disease and predicted all-cause mortality.(6) Fragmentation of the conducted QRS and paced ventricular electrogram fractionation have also been shown to identify patients at risk of

SCD.(7; 8) By extrapolation, fragmentation of the QRS complex of VEB may therefore also serve as a marker of risk.

We hypothesized that maximal VEQSI duration (VEQSI max), the number of VEB morphologies and maximal VEB fragmentation (VEB fragmentation max) would identify patients with prior MI compared with healthy subjects. We hypothesized that these VEB indices would distinguish IHD patients who have suffered life threatening events from those without a history of significant ventricular arrhythmia, independent of LVEF and conducted QRS interval.

METHODS

Patient characteristics

We recruited 189 patients with previous MI, identified from coronary care records and the ICD clinic of St George's Hospital, London. Acute MI was defined as symptoms and ECG changes consistent with infarction and elevated cardiac troponin. Inclusion criteria were MI at least 3 months before enrolment and cardiac catheterisation followed by revascularisation where appropriate. There were 151 patients (64±11 years; 74% male) without prior significant ventricular arrhythmia (MI-no VT/VF cohort) and 38 patients (66±9 years; 92% male) with secondary prevention ICD implantation for prior life threatening ventricular arrhythmia (MI-VT/VF cohort). Qualifying ventricular arrhythmic events in the MI-VT/VF cohort had occurred at least 3 months post-MI. Clinical assessment comprised documentation of medical history and medications; physical examination including blood pressure, pulse, height and weight; and blood sampling for renal function, brain natriuretic peptide (BNP) and inflammatory markers (C-reactive protein, CRP; and erythrocyte sedimentation rate, ESR).

Patients were compared with 60 normal controls (62±7 years; 70% male). These were individuals without known cardiac risk factors, prior history of cardiac disease or family history of inherited heart disease. These healthy volunteers had no significant abnormality on electrocardiogram (ECG) and transthoracic echocardiography.

The study had previously been given ethical approval by the Outer West London ethics committee and it complied with the Declaration of Helsinki.

Electrocardiography

Digital 10-second 12 lead ECGs were acquired using laptop based software (Cardiosoft™ GE Healthcare, UK) and reviewed at 10mm/mV and 25mm/s. Intervals including PR, RR, QRS and QT were recorded in milliseconds. The QT interval was corrected (QTc) using Bazett's formula. Pathological Q waves and QRS fragmentation (fQRS) were considered present when observed in ≥2 ECG leads in the same coronary artery territory. A Q wave was defined as ≥40ms in duration or >25% of the following R wave in voltage. fQRS included various RSR patterns, as previously described.(9) Ventricular paced QRS complexes were excluded from Q wave and fQRS analysis.

Holter monitoring

Holter monitoring was performed for a 24-hour period. Digital 10-electrode 12 channel recording devices with a sampling frequency of 1024Hz (CardioMem® CM 3000-12, Getemed, Germany) were applied in the Mason-Likar configuration. Analysis was performed on a workstation using commercial Holter analysis software (Cardioday®, Getemed, Germany).

All recordings were analysed by the same physician, blinded to the clinical diagnosis, who performed careful manual over-reading to eliminate artefact and correct the

automated identification of VEB and their classification by morphology. 11 traditional Holter ECG variables were selected for evaluation: VEB frequency, ventricular couplets, episodes of non-sustained ventricular tachycardia (NSVT), maximum heart rate during NSVT, minimum, mean and maximum heart rate, time domain indices of heart rate variability (HRV) (standard deviation of NN intervals, SDNN; and HRV triangular index), and frequency domain indices of HRV (high and low frequency power). NSVT was defined as ≥3 consecutive VEB. Frequent VEB were defined as VEB >1/minute.(10) Recordings with persistent atrial arrhythmia, persistent pacing, high frequency of ectopic beats and/or poor quality were excluded from HRV analysis.

All VEB in each recording were inspected. Differences in VEB morphology were identified with reference to bundle branch block pattern, QRS axis and R wave progression.(11) The number of different VEB morphologies was counted and recorded. VEQSI and VEB fragmentation were measured for each VEB morphology from a single representative QRS complex, chosen for the clarity of its onset and termination (figure 1). Fusion beats, couplets and NSVT were excluded from analysis. VEQSI measurements were made using electronic callipers on a simultaneous 12-derivation ECG segment at 20mm/mV and 100mm/s. We measured from the start of the QRS showing the earliest onset to the end of the QRS showing the latest termination. The duration of the broadest VEB was considered to be the VEQSI max of that patient.(6) Fragmentation measurements were made on a simultaneous 12-derivation ECG segment at 10mm/mV and 25mm/s. VEB fragmentation was defined as >2 notches in the R' or S waves and/or

2 notches separated by >40ms.(12) We recorded the total number of fragmented leads for each VEB morphology (excluding lead aVR). The VEB with the maximum number of fragmented leads was considered to be the VEB fragmentation max for that patient.

Effect of coupling interval on VEQSI

A subset of 10 Holter recordings with frequent VEB was reviewed in order to determine the effect of coupling interval on VEQSI. The predominant VEB morphology in each recording was identified and VEQSI was measured for the maximum and minimum coupling intervals and four additional coupling intervals within this range.

Echocardiography

Echocardiography was performed using standard views from the parasternal and apical windows to acquire 2D, colour Doppler and colour tissue Doppler (TDI) images (VIVID 7 with 4S-MHz probe, GE Vingmed Ultrasound, Horten, Norway). Three consecutive cardiac cycles were recorded for each view at end expiration. LV end diastolic diameter (LVEDD), LV end systolic diameter (LVESD) and LV wall thickness (LVWT) were derived from conventional 2D and M-mode images in the parasternal long and short axis views. LVEF was calculated by Simpson's biplane method using apical 4 and 2 chamber views. Results were compared with ASE/ESC guidelines to derive normal and abnormal values and to quantify the degree of abnormality present.(13)

Follow-up

Patients in the MI-VT/VF cohort were followed up for death and/or further life threatening events using patient records, ICD records and stored intracardiac electrograms. Events were considered life threatening when appropriate shock therapy was delivered for ventricular fibrillation (VF) or rapid sustained VT (rate >200 bpm).

Statistical Analysis

Statistical data analysis was carried out with SPSS 21.0 (SPSS Inc., Chicago, Illinois, USA). Univariate analysis of dichotomous, categorical and continuous data was performed to determine their influence or relationship with prior ventricular arrhythmia. The distribution of continuous variables was assessed for normality using Shapiro-Wilk test. Comparison between groups of continuous data was carried out via independent samples t-test after controlling for equality of variance using Levene's statistic, or Mann-Whitney U test where appropriate. Chi square test or Fisher's exact test were used for categorical data. Several models of multivariate regression analysis were made using all available variables and the most significant markers of prior life threatening ventricular arrhythmia were established using forward stepwise (Likelihood Ratio) logistic regression analysis. The multivariate analysis was validated using a bootstrap method with 1000 repeat samples from the dataset. Receiver operator characteristics (ROC) curve analysis was used to determine an optimal cut-off value for VEQSI max. Correlations between distributions were made using the Spearman method. A two-tailed p value <0.05 was considered significant.

RESULTS

Comparison of normal controls and patients with prior myocardial infarction

The VEB indices were all greater in patients with previous MI compared with normal controls: VEQSI max (185±26ms vs 164±16ms; p<0.001); number of VEB morphologies (3±3 vs 2±2; p<0.001); and VEB fragmentation max (7±5 vs 2±4; p<0.001; table 1).

Patients with prior myocardial infarction: Comparison of those with and those without prior life threatening ventricular arrhythmia

Patient characteristics

At the time of assessment, timing of the initial MI was more remote for the cohort with prior life threatening events (MI-VT/VF) than the cohort without prior significant ventricular arrhythmia (MI-no VT/VF). Patients in the MI-VT/VF cohort included more men, with a higher New York Heart Association (NHYA) functional class, BNP, urea and creatinine levels and more frequent use of antiarrhythmic medications (table 2).

Electrocardiogram and echocardiogram characteristics

The conducted QRS duration was longer in MI-VT/VF patients than MI-no VT/VF patients (112±45 vs 94±14; p<0.001). Other ECG characteristics were similar. LVEF was lower (40±17 vs 55±17; p<0.001) and LVEDD was higher (58±1 vs 49±1; p<0.001) in the MI-VT/VF cohort compared with the MI-no VT/VF cohort (table 2).

Holter characteristics

Ventricular ectopic beats were present in 97% of MI-VT/VF patients and 91% of MI-no VT/VF patients. The 24-hour VEB count was higher in the MI-VT/VF cohort than the MI-no VT/VF cohort (244±714 vs 30±315; p<0.001). Ventricular couplets (3±11 vs 0±1; p<0.001) and NSVT (34% vs 11%; p=0.001) were more frequent in MI-VT/VF patients than MI-no VT/VF patients (table 2).

Maximal ventricular ectopic QS interval (VEQSI max)

VEQSI max was longer in MI-VT/VF patients compared with MI-no VT/VF patients (214±20ms vs 177±22ms; p<0.001; table 2 and figure 2). When patients were subdivided according to LVEF (normal/mildly impaired >45%; moderately impaired 35-45%; severely impaired <35%) and QRS duration (<120ms; ≥120ms), VEQSI max remained longer in the MI-VT/VF cohort within all subdivisions of LVEF and conducted QRS interval (table 3).

There was no significant change in VEQSI max within the physiological range of coupling intervals demonstrated during Holter monitoring (figure 3). In particular VEQSI max did not prolong at shorter coupling intervals.

Number of ventricular ectopic beat (VEB) morphologies

The number of VEB morphologies was greater in MI-VT/VF patients than MI-no VT/VF patients (6±4 vs 3±2; p<0.001; table 2).

Maximal VEB fragmentation (fragmentation max)

VEB fragmentation max was greater in MI-VT/VF patients than MI-no VT/VF patients (8±3 vs 6±4; p=0.004; table 2).

Markers of prior life threatening events

Several univariate markers of prior significant ventricular arrhythmia were identified including the VEB indices (VEQSI max, number of VEB morphologies, VEB fragmentation max), blood markers (BNP, urea, creatinine), conducted QRS duration, Holter variables (VEB count, couplet count, presence of complex VEB, NSVT) and echocardiographic parameters (LVEDD, LVEF; table 2). After multivariate logistic regression analysis only VEQSI max and LVEDD remained independent markers. VEQSI max demonstrated the strongest association, with a 1ms increase in VEQSI max increasing the odds of prior life threatening events by a factor of 1.06 (95% Confidence Interval (CI) 1.03-1.09; p<0.001; table 4). The bootstrap method confirmed that the magnitude of association for VEQSI max and LVEDD with prior significant ventricular arrhythmia withstood resampling and is unlikely to be incidental.

The probability of prior significant ventricular arrhythmia increased with VEQSI max duration. ROC curve analysis was used to determine the optimal VEQSI max cut-off value associated with prior life threatening events. VEQSI max >198ms had 86% sensitivity, 85% specificity, 62% positive predictive value (PPV) and 96% negative predictive value (NPV) for this (Area Under Curve (AUC) 0.90; 95% CI 0.85-0.95; table 5

and figure 4) with an OR 37.4; 95% CI 13.0-107.5. VEQSI max was the superior marker compared with LVEDD (AUC 0.90; SE 0.028 vs AUC 0.81; SE 0.04 respectively).

Relationship between VEQSI max, the number of VEB morphologies, VEB fragmentation max and LV structural changes

There was moderate correlation between VEQSI max and LVEDD (r_s 0.59; p<0.001) and VEQSI max and LVEF (r_s -0.58 p<0.001). Correlations between number of VEB morphologies and LVEDD (r_s 0.46; p<0.001), number of VEB morphologies and LVEF (r_s -0.42; p<0.001), VEB fragmentation max and LVEDD (r_s 0.38; p<0.001) and VEB fragmentation max and LVEF (r_s -0.34; p<0.001) were less strong but still significant.

Antiarrhythmic Drug Therapy

In the MI-VT/VF cohort there were 12 patients receiving long-term amiodarone therapy. As amiodarone use can influence conduction properties, additional analysis was performed following the exclusion of these patients. VEQSI max remained significantly longer in the MI-VT/VF cohort compared with the MI-no VT/VF cohort (210±16ms and 172±21ms respectively; p<0.001). No patient received any other class III antiarrhythmic medication and none received any class I antiarrhythmic.

Follow-up

During a mean follow-up period of 48±11 months, 10 patients (26%) in the MI-VT/VF cohort suffered further VT/VF events requiring defibrillation and 7 patients (18%) died.

These patients all had VEQSI max duration >198ms. VEQSI max was longer in MI-VT/VF patients that died or had subsequent VT/VF events requiring defibrillation than in the MI-VT/VF patients who survived event free (221±19ms and 205±20ms respectively; p=0.028).

DISCUSSION

In this study we have shown that VEB indices: VEQSI max, the number of VEB morphologies and VEB fragmentation max identified patients with prior MI compared with healthy subjects. In IHD patients, these VEB indices distinguished those who had suffered life threatening events (MI-VT/VF) from those without a history of significant ventricular arrhythmia (MI-no VT/VF). VEQSI max was greater in MI-VT/VF patients irrespective of LVEF and conducted QRS interval and it was the strongest independent marker for prior life threatening ventricular arrhythmia.

We have previously demonstrated that in unselected patients attending for outpatient Holter monitoring, VEQSI max correlated with presence and severity of structural heart disease and multiple VEB morphologies predicted all-cause mortality.(6) ECG data recorded during cardiac catheterisation has shown that broadly notched VEB ≥160ms are a marker of LV dilatation and impairment.(14) Slowed conduction through diseased myocardium has been shown to result in longer QRS duration during VT in patients with ARVC and data from electrophysiological studies has shown that longer VEB duration is associated with myocardial scar.(15–17) Broader VEB have also been associated with development of non-ischaemic cardiomyopathy.(18–20) The greater VEQSI max demonstrated in our IHD patients with prior life threatening events likely reflects a greater amount of underlying scar and slowed conduction. The incidence of Q wave MI was also higher in these MI-VT/VF patients compared with MI-no VT/VF patients, albeit not significantly.

In this study although increased VEQSI max duration correlated with decreased LVEF, it was an independent variable that distinguished IHD patients with prior life threatening events from those without significant ventricular arrhythmia. Multivariate logistic regression analysis showed it to be the most significant and consistent marker for this. VEQSI max >198ms had high sensitivity and specificity for the identification of post-MI patients with a previous life threatening event. In addition VEQSI max was greater in IHD patients with prior significant ventricular arrhythmia who died or suffered a subsequent life threatening event compared with those who survived with no further significant ventricular arrhythmia during the follow-up period of 48 months. This suggests that VEQSI max may offer incremental value for risk stratification in patients following MI.

Fragmentation of the conducted QRS has been shown to correlate with myocardial scar and predict risk in ischaemic cardiomyopathy and BrS.(7; 21) In HCM increased fractionation of paced RV electrograms has been shown to correlate with the risk of VF.(8; 22) In a prospective study paced ventricular electrogram fractionation (PEFA) also predicted patients at risk of SCD with greater accuracy than non-invasive techniques.(23) We may have therefore expected fragmentation of the VEB to serve as a diagnostic and risk stratification tool in cardiomyopathy but in our multivariate analysis it did not feature, apparently due to the superior predictive power of VEQSI max.

Comparison of VEQSI max, the number of VEB morphologies and VEB fragmentation max as indices for previous significant ventricular arrhythmia showed that VEQSI max was superior. It is also more convenient. Although 12-lead Holter monitoring improves the ability to differentiate between VEB morphologies compared to older 3-derivation systems, QRS axis is subject to change with posture and the laborious manual over-reading required to correct for this is likely to also limit clinical applicability. Measurement of VEB fragmentation by the methods that we have used is not possible using a standard 3 or 5 lead Holter system, but requires a 12 lead system, limiting its utility in clinical practice. The automated measurement of VEQSI max is likely to be more robust than that of VEB fragmentation or the number of morphologies, and we have previously demonstrated that this index can be determined using Holter monitoring systems with fewer leads.(6) We therefore consider VEQSI max to be the most useful of the three indices.

Randomised clinical trials have established that ICD therapy can improve survival for individuals at risk of SCD.(1) It is therefore important to correctly identify at risk individuals for treatment. In patients with IHD, reduced LVEF remains the best established predictor of SCD but this is imperfect.(1; 2) The majority of SCD occurs in those with low, intermediate or no risk factors and in primary prevention trials which selected individuals for ICD therapy predominantly on the basis of reduced LVEF, only one third had appropriate device therapy over the 3-5 year follow-up.(1; 2; 4)

Prospective follow-up data is needed to determine the potential role for combining VEQSI max with LVEF and conducted QRS interval in risk analysis algorithms as well as the optimal cut-off value for VEQSI max. Our dataset does demonstrate overlap within the 180-200ms range between the two groups. From a clinical perspective a cut-off value of 198ms appears most useful. This affords high sensitivity whilst maintaining good specificity. When selecting patients for prophylactic ICD implantation, high sensitivity and identification of true positives, those at highest risk of ventricular arrhythmia, would appear to be the more important factor. Longer prospective follow-up will be important to determine outcomes of patients with VEQSI max >198ms, particularly those in the MI-no VT/VF cohort.

STUDY LIMITATIONS

Consecutive patients treated for MI at St George's Hospital and all IHD patients under follow-up in the ICD clinic with secondary prevention devices were invited to take part in the study. Only one third agreed which introduces a possibility of selection bias. Our data showed VEQSI max was a stronger marker for prior life threatening events than LVEF but it must be noted that the MI-VT/VF sample size was modest and included few patients with low LVEF. In addition all patients were recruited prospectively, but the majority of events occurred before recruitment and this is a retrospective study. Prospective follow-up data is required to determine the outcome of patients with longer VEQSI max without a history of serious arrhythmia at the time of assessment.

CONCLUSION

The maximal ventricular ectopic QRS interval (VEQSI max) distinguishes ischaemic heart disease patients who have suffered life threatening events from those without a history of significant ventricular arrhythmia. VEQSI max shows promise as an additional risk stratification tool for sudden death to be considered for use in combination with existing indices.

CLINICAL COMPETENCIES

Reduced left ventricular ejection fraction (LVEF) is the best established predictor of sudden death in patients with ischaemic heart disease (IHD), but the majority of events occur in those with LVEF >35%. In this study, the maximal ventricular ectopic QRS

interval (VEQSI max) was the strongest marker of prior life threatening ventricular arrhythmia in post-myocardial infarction patients.

TRANSLATIONAL OUTLOOK

VEQSI max shows promise as an additional risk stratification index in ischaemic heart disease. Prospective follow-up data in a larger cohort is required. This will be of particular interest in patients with LVEF 35-50%.

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FIGURE LEGENDS

Figure 1

Measurement of the ventricular ectopic QRS interval (VEQSI). Panel A demonstrates a ventricular ectopic beat (VEB) from a patient with prior myocardial infarction (MI) and no significant ventricular arrhythmia (MI-no VT/VF cohort). VEQSI measures 173ms. Panel B demonstrates a VEB from a patient with prior MI and life threatening ventricular arrhythmia (MI-VT/VF cohort). VEQSI measures 213ms. In this example the calibration has a gain of 10mm/mV and speed of 100mm/s.

Figure 2

The maximal ventricular ectopic QRS interval (VEQSI max) in patients with prior myocardial infarction (MI) and life threatening ventricular arrhythmia (MI-VT/VF cohort) and patients with prior MI but no history of significant ventricular arrhythmia (MI-no VT/VF cohort). The notches for the box plots do not overlap which can be regarded as strong evidence that previous life threatening arrhythmic events are associated with significantly longer VEQSI max.

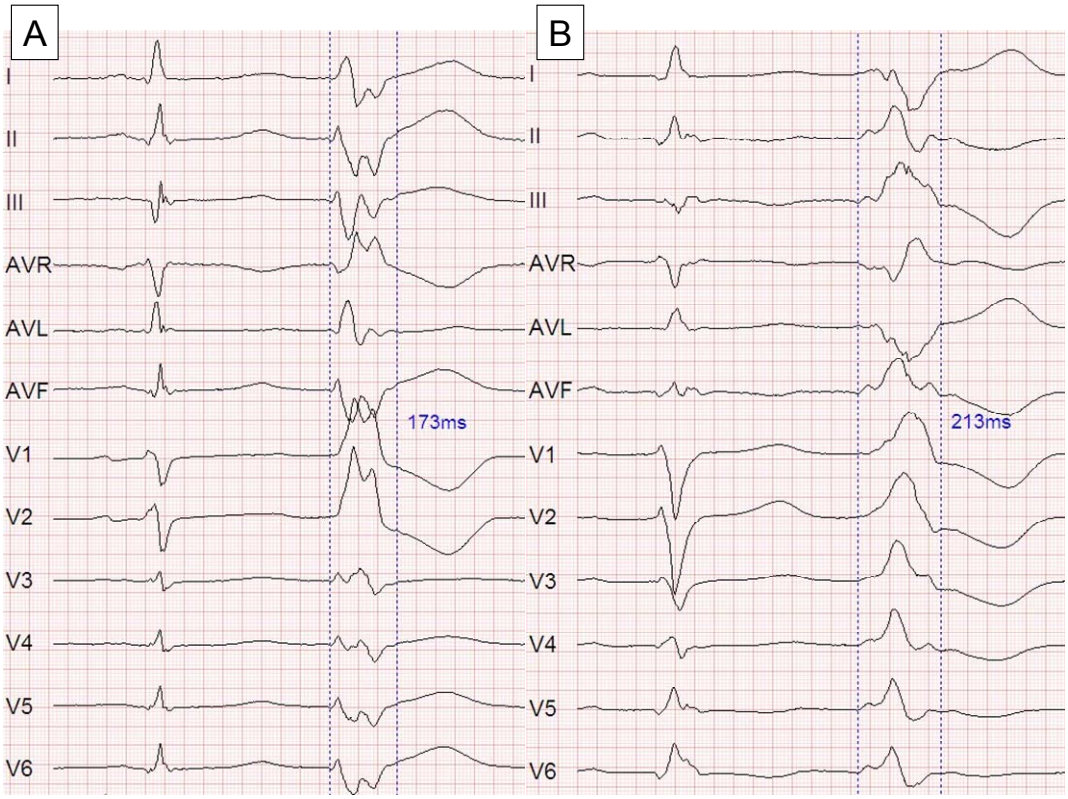
Figure 3

Variation of the ventricular ectopic QRS interval (VEQSI) with coupling interval in ventricular ectopic beats (VEB) with a uniform morphology. There was no significant change in VEQSI max within the physiological range of coupling intervals demonstrated during Holter monitoring.

Figure 4

Receiver operator characteristics (ROC) curves for the maximal ventricular ectopic QRS interval (VEQSI max) duration and left ventricular end diastolic diameter (LVEDD) in the differentiation of ischaemic heart disease (IHD) patients with and without a history of significant ventricular arrhythmia (MI-VT/VF and MI-no VT/VF cohorts respectively). VEQSI max was a superior marker compared with LVEDD (AUC 0.90; SE 0.028 vs AUC 0.81; SE 0.04 respectively). VEQSI max >198ms had 86% sensitivity and 85% specificity for identification of patients with prior myocardial infarction (MI) and life threatening ventricular arrhythmia (MI-VT/VF cohort).

Figure 1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AVF
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V2
V3
V4
V5
V6
213ms

Figure 2

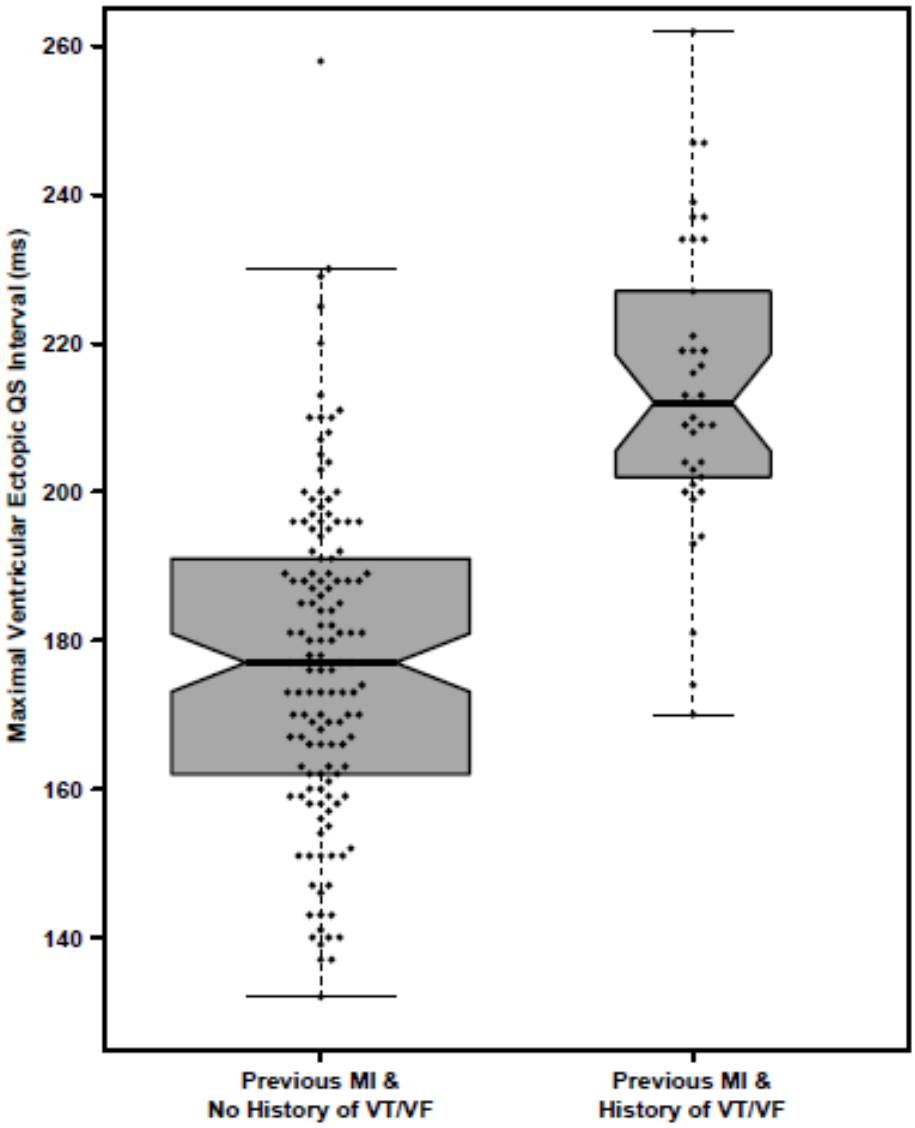

Maximal Ventricular Ectopic QS Interval (ms)
260
240
220
200
180
160
140
Previous MI &
No History of VT/VF
Previous MI &
History of VT/VF

Figure 3

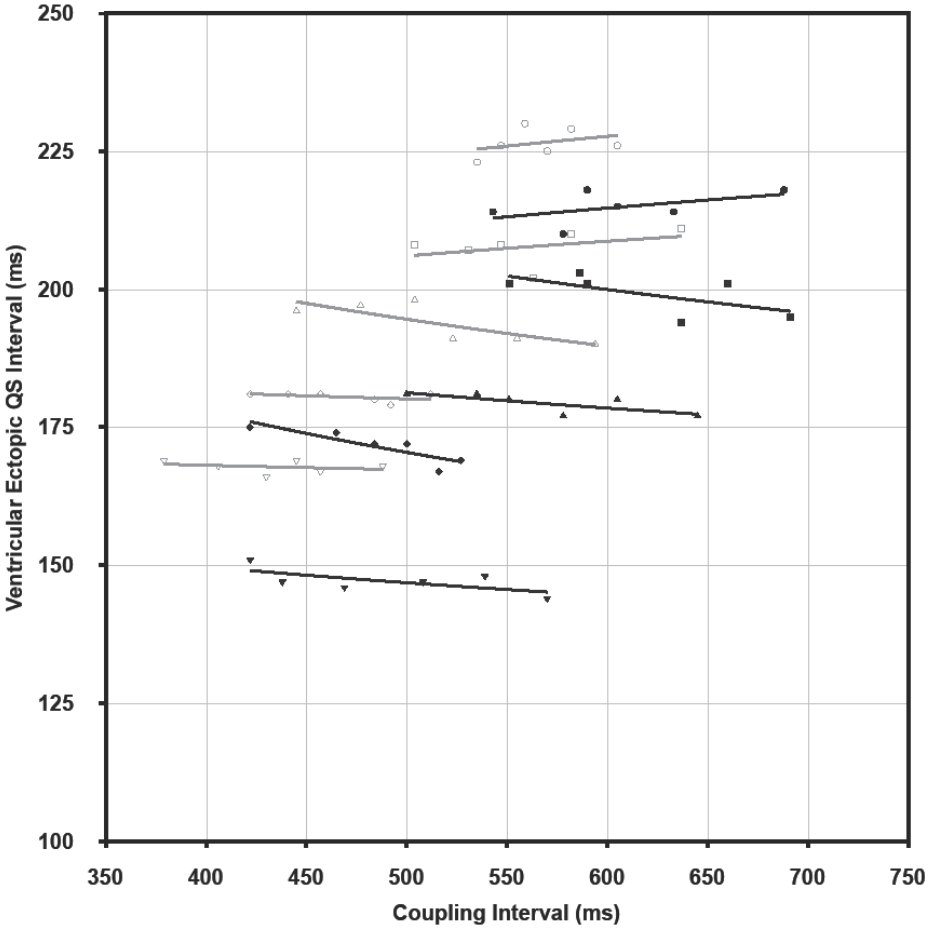
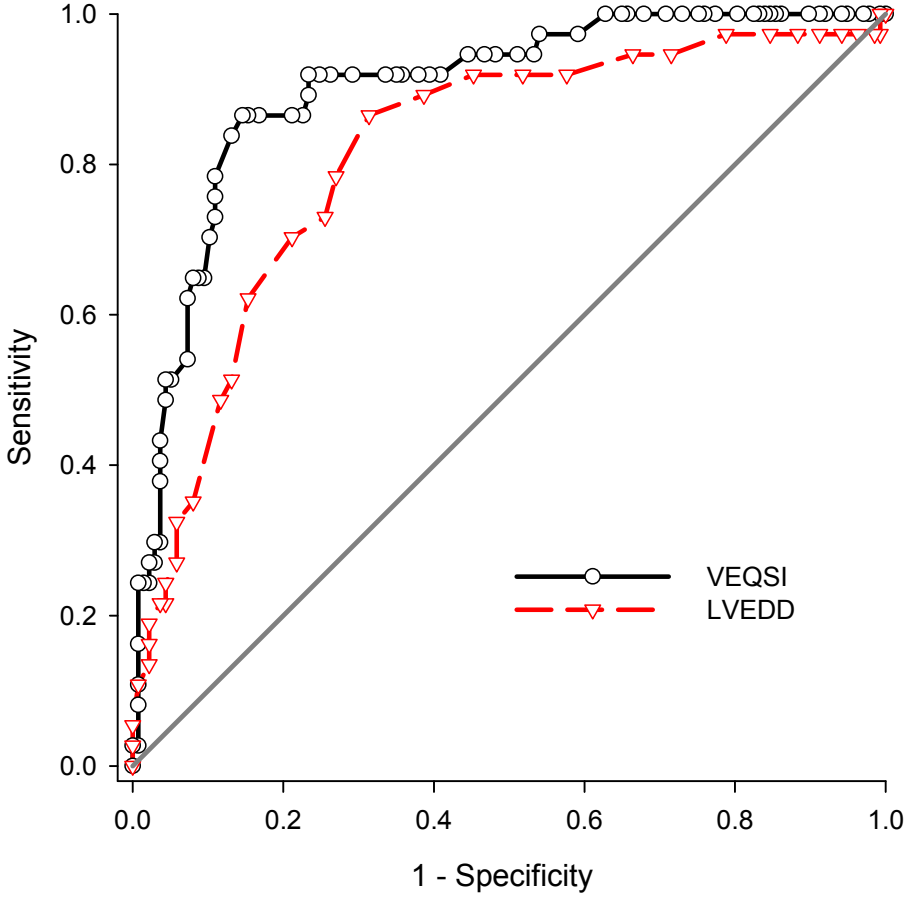

250
225
200
175
150
125
100
Ventricular Ectopic QS Interval (ms)
350
400
450
500
550
600
650
700
750
Coupling Interval (ms)

Figure 4


1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
1 - Specificity
VEQSI
LVEDD

TABLES

Table 1 Comparison of ventricular ectopic indices in normal controls and patients with prior myocardial infarction.

	Normal controls (n=60)	Patients with prior MI (n=189)	p-value
Age (years; mean±SD)	62±7	64±11	0.113
Sex (male; %)	70	78	0.229
VEB present (%)	83	92	0.081
VEQSI max (ms; mean±SD)	164±16	185±26	**<0.001**
VEB morphologies (n; median±IQ range)	2±2	3±3	**<0.001**
VEB fragmentation max (n; median±IQ range)	2±4	7±5	**<0.001**

MI, myocardial infarction; VEB, ventricular ectopic beat; VEQSI, ventricular ectopic QRS interval

Table 2 Patients with prior myocardial infarction. Comparison of clinical characteristics, electrocardiographic and echocardiographic data in those with and those without prior life threatening ventricular arrhythmia.

	MI-VT/VF (n=38)	MI-no VT/VF (n=151)	p-value
Age (years; mean±SD)	66±9	64±11	0.274
Sex (male; %)	92	74	**0.017**
Medications (%)			
• Beta-blocker	95	76	**0.009**
• Calcium channel blocker	0	9	0.061
• ACE inhibitor	95	90	0.560
• Amiodarone	32	0	**<0.001**
• Digoxin	16	1	**<0.001**
Time from MI to assessment (months; mean±SD)	137±114	18±18	**<0.001**
Location of infarct segments (%)			
• Anterior	50	33	0.053
• Inferior	21	26	0.543
• Lateral	3	8	0.471
• Posterior	0	1	1.000
• Greater than one territory	26	32	0.466
NYHA class (median±IQ range)	2±1	1±1	**0.01**
Pulse (bpm; median±IQ range)	58±17	62±13	0.341
Systolic BP (mmHg; median±IQ range)	130±28	130±29	0.407
Diastolic BP (mmHg; median±IQ range)	80±15	80±16	0.736
BMI (median±IQ range)	28±8	28±5	0.522
Plasma			
• BNP (median±IQ range)	982±2073	278±600	**<0.001**
• Urea (median±IQ range)	7.7±13	5.9±3	**0.018**
• Creatinine (median±IQ range)	106±74	83±19	**<0.001**
• CRP (median±IQ range)	11±16	10±12	0.560
• ESR (median±IQ range)	24±24	12±22	0.157
Conducted QRS duration (ms; median±IQ range)	112±45	94±14	**<0.001**
QTc interval (ms; median±IQ range)	422±47	416±34	0.108
Q waves* (n%)	24 (75)	89 (60)	0.097
QRS fragmentation* (n%)	21 (55)	79 (52)	0.745
Mean HR (bpm; median±IQ range)	64±13	67±15	0.06

Subjects with VEB present (n%)	37 (97)	137 (91)	0.176
Number of VEB (n; median±IQ range)	244±714	30±315	**<0.001**
Number of couplet(s) (n%)	3±11	0±1	**<0.001**
Presence of frequent VEB (n%)	7 (18)	12 (8)	0.055
Presence of complex VEB (n%)	37 (97)	114 (76)	**0.003**
Presence of NSVT (n%)	13 (34)	17 (11)	**0.001**
SDNN (median±IQ range)	138±70	135±55	0.757
HRV triangular index (median±IQ range)	28±17	28±11	0.164
HFP (median±IQ range)	1.46E-08±2.19E-08	8.03E-09±3.52E-08	0.447
LFP (median±IQ range)	1.87E-08±4.06E-08	2.74E-08±1.30E-07	0.247
LVEDD (mm; median±IQ range)	58±1	49±1	**<0.001**
LVEF (%; median±IQ range)	40±17	55±17	**<0.001**
VEB morphologies (n; median±IQ range)	6±4	3±2	**<0.001**
VEQSI max (ms; mean±SD)	214±20	177±22	**<0.001**
VEB fragmentation max (n; median±IQ range)	8±3	6±4	**0.004**

*Data not available for all patients due to ventricular pacing/bundle branch block

MI-VT/VF, patients with prior myocardial infarction and life threatening ventricular arrhythmia; MI-no VT/VF, patients with prior myocardial infarction and no significant ventricular arrhythmia; ACE, Angiotensin-converting enzyme; NYHA, New York Heart Association functional class; BP, blood pressure; BMI, body mass index; BNP, brain natriuretic peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HR, heart rate; VEB, ventricular ectopic beat; NSVT, non-sustained ventricular tachycardia; VEQSI, ventricular ectopic QRS interval; SDNN, standard deviation of NN intervals; HRV, heart rate variability; HFP, high frequency power; LFP, low frequency power; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction

Table 3 The maximal ventricular ectopic QRS interval (VEQSI max) in patients with and without prior life threatening ventricular arrhythmia stratified by left ventricular ejection fraction (LVEF) and conducted QRS interval

	MI-VT/VF VEQSI max (ms; mean±SD)	MI-no VT/VF VEQSI max (ms; mean±SD)	p-value
LVEF			
• Normal/Mildly impaired (>45%)	201±23	174±21	**<0.001**
• Moderately impaired (35-45%)	216±18	185±21	**<0.001**
• Severely impaired (<35%)	221±18	194±22	**0.004**
Conducted QRS interval			
• <120ms	206±16	176±22	**<0.001**
• ≥120ms	228±18	188±20	**<0.001**

MI-VT/VF, patients with prior myocardial infarction and life threatening ventricular arrhythmia; MI-no VT/VF, patients with prior myocardial infarction and no significant ventricular arrhythmia

Table 4 Markers of prior significant ventricular arrhythmia in patients with ischaemic heart disease. The variables that remained significant following multivariate and logistic regression analysis are shown in the table.

	Multivariate Analysis						Bootstrap			
	B	SE	Wald	p	OR	95% CI	SE	p	Bias	95% CI
LVEDD (cm)	0.864	0.673	1.65	0.2	2.37	0.63-8.87	166	0.25	18.2	-2.73-147.6
VEQSI max (ms)	0.105	0.027	14.7	**<0.001**	1.11	1.05-1.17	12.5	**0.001**	2.01	0.082-16.91
Constant	-18.2	7.08	6.6	0.01						
	Logistic Regression Analysis (final model)									
	B	SE	Wald	p	OR	95% CI				
LVEDD (cm)	0.835	0.400	4.35	**0.037**	2.31	1.05-5.05				
VEQSI max (ms)	0.060	0.014	18.2	**<0.001**	1.06	1.03-1.09				
Constant	-17.9	3.26	30.2	0.000000						

LVEDD, left ventricular end diastolic diameter; VEQSI max, maximal ventricular ectopic QRS interval; B, regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval

Table 5 The maximal ventricular ectopic QRS interval (VEQSI max) cut-off values for identification of life threatening ventricular arrhythmia in patients with ischaemic heart disease.

	VEQSI max 195ms	**VEQSI max 198ms**	VEQSI max 200ms
AUC	0.82	**0.90**	0.85
Sensitivity	0.86	**0.86**	0.84
Specificity	0.77	**0.85**	0.87
PPV	0.51	**0.62**	0.63
NPV	0.95	**0.96**	0.95
OR (95% CI)	21.9 (7.86-60.9)	**37.4 (13.0-107.5)**	34.2 (12.5-93.3)
Accuracy	0.79	**0.86**	0.86
Prevalence	0.21	**0.21**	0.21
LR (95% CI)	3.82 (2.73-5.34)	**5.92 (3.87-9.06)**	6.38 (4.05-10.0)

AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; OR, odds ratio; CI, confidence interval; LR, likelihood ratio