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# The ventricular ectopic QRS interval (VEQSI): Diagnosis of arrhythmogenic right ventricular cardiomyopathy in patients with incomplete disease expression

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## Abstract

### Background

The ventricular ectopic QRS interval (VEQSI) has been shown to identify structural heart disease and predict mortality. In arrhythmogenic right ventricular cardiomyopathy (ARVC) early diagnosis is difficult with current methods and life-threatening arrhythmias are common and difficult to predict.

### Objectives

To assess the utility of ventricular ectopic indices including VEQSI in ARVC diagnosis.

### Methods

We studied 70 patients with ARVC; 30 with definite disease (47±12 years; 60% male); 40 with incomplete disease expression (44±18 years; 44% male); 116 healthy controls (40±15 years; 56% male); and 26 patients with normal heart right ventricular outflow tract (RVOT) ectopy (46±17 years; 27% male). The duration of the broadest ventricular ectopic beat during 12-lead Holter monitoring was recorded as VEQSI max.

### Results

VEQSI max was associated with age and gender, not conducted QRS duration. Adjusted VEQSI max was greater in ARVC patients than control groups. In healthy males (44.5 years) estimated VEQSI max was 163ms (95%CI 159ms-167ms); in definite ARVC 212ms (95%CI 206ms-217ms); in incompletely expressed ARVC 204ms (95%CI 199ms-210ms); and in normal heart RVOT ectopy 171ms (95%CI 165ms-178ms). VEQSI max >180ms had 98% sensitivity

and specificity for the diagnosis of ARVC (AUC 0.99; 95%CI 0.980-0.998). In our incompletely expressed ARVC patients, VEQSI max >180ms identified 88% as affected.

**Conclusion**

VEQSI max distinguishes ARVC patients, including those with incomplete disease expression, from healthy controls and patients with normal heart RVOT ectopy.

**Keywords**

arrhythmogenic right ventricular cardiomyopathy; implantable cardioverter-defibrillator; sudden cardiac death; ventricular ectopic QRS interval (VEQSI); ventricular ectopic beat

## Introduction

With intact cardiac conduction the QRS may remain narrow in the presence of abnormal ventricular myocardium. Ventricular ectopic beats (VEB) are usually conducted through the myocardium with limited participation of specialized conduction tissue, so the QRS interval of VEB may provide an index of myocardial condition and risk of sudden cardiac death (SCD).(1) We have previously demonstrated that the ventricular ectopic QRS interval (VEQSI) is associated with mortality in an unselected population.(2) In ischaemic heart disease, VEB duration and complexity has been shown to correlate with left ventricular (LV) dilatation and dysfunction.(3)

Arrhythmogenic right ventricular cardiomyopathy (ARVC) manifests with an initial concealed phase in which ventricular arrhythmia can occur, but ventricular structure and function is preserved. There is no single diagnostic test for ARVC; diagnosis relies on meeting Task Force criteria.(4) Electrocardiographic capture of ventricular tachycardia (VT) with left bundle branch block (LBBB) superior axis is the sole major arrhythmia criterion, but a minority of affected patients exhibit VT at any given assessment and some never develop VT.

ARVC shares common features with normal heart right ventricular outflow tract (RVOT) ectopy: both affect young people and are associated with LBBB morphology ventricular arrhythmia, frequently precipitated by exercise. Differentiation between conditions is important to guide therapy and follow-up

and assess SCD risk. Whereas RVOT ectopy appears benign, ARVC is associated with risk of SCD.(5, 6)

During the concealed phase, ARVC diagnosis is difficult due to diffuse structural abnormalities. Imaging demonstrates normal cardiac appearance or subtle non-diagnostic anomalies. Electrical changes appear to predate structural changes and VEB are frequent.(7,8) We hypothesized that VEB indices: VEQSI, number of VEB morphologies and VEB fragmentation would provide markers for presence and severity of abnormal ventricular structure and function and a measure of the risk of ventricular arrhythmia.(1) We hypothesized that VEB indices may be useful in early ARVC diagnosis.

## Methods

### Patient characteristics

ARVC patients were identified from databases at St George's Hospital London, the Heart Hospital London and the University of Bologna. Their clinical data were analysed for contemporaneous disease categorization by Task Force criteria (supplementary table 1).(4) 30 patients (47±12 years; 60% male) with definite disease were recruited. Amongst this group, 17 had prior life-threatening arrhythmia (cardiac arrest and/or sustained VT resulting in haemodynamic collapse). 40 patients (44±18 years; 43% male) with incompletely expressed ARVC were recruited. These patients had borderline clinical phenotype consisting of one minor Task Force criterion, non-diagnostic cardiac imaging and definite ARVC confirmed in a first-degree relative using Task Force criteria and/or at post-mortem. None was symptomatic (table 1).

ARVC patients were compared with 116 normal controls (40±15 years; 56% male). These were individuals without cardiac disease or risk factors, family history of inherited heart disease or significant abnormality on electrocardiogram (ECG) and echocardiography. A second control group was recruited with 26 patients under follow-up/pre-ablation for RVOT ectopy (46±17 years; 27% male) who also had normal ECGs and echocardiograms (table 1).

LV involvement was defined as ejection fraction ≤50% and/or late enhancement on cardiac magnetic resonance imaging (CMR). Informed consent was obtained

from each patient. The study received local ethics committee approval and complied with the Declaration of Helsinki.

**Electrocardiography**

Digital 10-second 12-lead ECGs were acquired (Cardiosoft™ GE Healthcare, UK) and reviewed at 10mm/mV and 25mm/s. PR, RR, QRS and QT intervals were recorded. The QT-interval was corrected (QTc) using Bazett's formula. Presence of epsilon waves and T-wave inversion in leads V1-V6 and II, III and aVF was noted.

**Holter monitoring**

Holter monitoring was performed for 24hours. Digital 10-electrode 12-channel devices with sampling frequency of 1024Hz (CardioMem® CM3000-12, Getemed, Germany) were applied in the Mason-Likar configuration. Analysis was performed on a commercial workstation (Cardioday®, Getemed, Germany). All recordings were analysed by the same physician, blinded to the clinical diagnosis, who performed manual over-reading to eliminate artifact and correct the automated identification of VEBs and classification by morphology. The following Holter variables were evaluated: minimum, mean and maximum heart rate; VEB presence, frequency, site of origin; VT presence, frequency, site of origin. Definitions included: VT ≥3 consecutive VEB; frequent VEB >500/24hours. VEB and VT types/origins were classified according to Task Force criteria: LBBB

superior axis, LBBB inferior axis, right-bundle branch block (RBBB) superior axis or RBBB inferior axis.(4)

Three novel VEB indices were examined: VEQSI, number of VEB morphologies and VEB fragmentation. All VEBs in each recording were inspected. Differences in VEB morphology were identified with reference to bundle branch block pattern, QRS axis and R-wave progression.(9) Fusion beats, couplets and VT were excluded from VEB analysis. The number of VEB morphologies was counted and recorded. VEQSI and VEB fragmentation were measured for each VEB morphology from a representative QRS complex, chosen for the clarity of onset and termination (figure 1).

VEQSI measurements were made using electronic calipers on a simultaneous 12-derivation ECG segment (20mm/mV, 100mm/s) from the start of the QRS showing the earliest onset to the end of the QRS showing the latest termination across all leads. The duration of the broadest VEB was VEQSI max.(2) Fragmentation measurements were made on a simultaneous 12-derivation ECG segment (10mm/mV, 25mm/s). VEB fragmentation was defined as >2 notches in the R' or S waves and/or 2 notches separated by >40ms.(10) The maximum number of fragmented leads was fragmentation max.

Inter-observer and intra-observer variability were measured using a subset of 22 Holter recordings analysed blindly by three different observers and on two

occasions by one observer. Inter-observer variability intraclass correlation coefficients (ICC) were 0.93 for VEQSI max, 0.90 for VEB morphologies and 0.90 for VEB fragmentation max. Intra-observer variability ICC were 0.97 for VEQSI max, 0.99 for VEB morphologies and 0.95 for VEB fragmentation max.

**Statistical analysis**

Statistical tests were performed using STATA (StataCorp. 2011 Stata Statistical Software:Release 12. College Station, TX:StataCorp LP.) and R (http://www.R-project.org/). Summary statistics were presented: means, medians, standard deviations (SD), inter-quartile ranges (IQR) for continuous variables and proportions for categorical variables. The Shapiro–Wilk test was used to assess normality of data.

Univariate and multivariable analyses were performed to investigate the relationship between VEB indices: VEQSI max, number of VEB morphologies and VEB fragmentation max with age, gender, conducted QRS duration and disease group. For these analyses, only patients with VEB could be included. A parsimonious model was derived. Techniques included forward regression, backward elimination and a combination of both. An alpha-level of <0.05 was considered significant. Potential interaction effects were considered, kept in the model if statistically or clinically significant and interpreted accordingly. Residual plots were used to assess adequacy of the models and assumptions. Predictions stratified by age, gender and disease group were presented.

VEB morphologies were categorized as follows: 1=1-2 morphologies (64%); 2=3 morphologies (10%); 3=≥4 morphologies (26%). VEB fragmentation was categorized as follows: 1=fragmentation max 1-2 (53%); 2=fragmentation max 3-4 (19%); 3=fragmentation max 5-6 (26%); 4=fragmentation max ≥7 (17%). Associations with other variables were expressed in terms of proportional odds for those in groups $>k$ versus those in groups $\leq k$, where $k$ is the level of the response variable defined above.

Receiver operating characteristic (ROC) curve analysis was used to examine the extent to which VEB indices can be used as markers of disease and establish diagnostic ranges. ARVC patients were compared with normal controls and RVOT ectopy patients. Accuracy was measured by area under the curve (AUC) and the corresponding results were compared. Thresholds for optimum sensitivity and specificity of each VEB index were derived, with results adjusted for age and gender.

## Results

### *Holter characteristics*

VEB were present in the majority of subjects (table 1). In normal controls the commonest VEB morphology was RBBB superior axis suggesting an LV origin. In ARVC the commonest VEB morphology was LBBB superior axis and in RVOT ectopy the commonest VEB morphology was LBBB inferior axis, suggesting right ventricular (RV) origins.

VT occurred in 30% definite ARVC, 15% incompletely expressed ARVC and 8% RVOT ectopy patients. In definite ARVC the commonest VT morphologies were LBBB inferior and LBBB superior axis (44% patients with VT). In incompletely expressed ARVC the commonest VT morphology was LBBB superior axis (67% patients with VT). In RVOT ectopy all VT was LBBB inferior axis.

### *VEQSI max*

VEQSI max was longer in definite and incompletely expressed ARVC patients than normal controls and RVOT ectopy patients (209±18ms, 200±12ms, 159±16ms and 165±14ms respectively; table 1; figure 2; raw data).

VEQSI max was associated with age and gender, not conducted QRS duration (table 2). Adjusted VEQSI max remained greater in ARVC patients than control groups. In healthy males (average age 44.5 years) estimated VEQSI max was 163ms (95%CI 159ms-167ms); in definite ARVC 212ms (95%CI 206ms-217ms);

in incompletely expressed ARVC 204ms (95%CI 199ms-210ms); and in RVOT ectopy 171ms (95%CI 165ms-178ms; supplementary table 2).

***VEB morphologies***

There were more VEB morphologies in definite and incompletely expressed ARVC patients than normal controls and RVOT ectopy patients (5±4, 3±4, 1±1 and 2±1 respectively; table 1; raw data).

The number of VEB morphologies was associated with age and gender, not conducted QRS duration (table 2). Adjusted VEB morphologies remained greater in ARVC patients than control groups. In incomplete ARVC the odds of ≥4 (vs <4) VEB morphologies was 11.1 times greater than in normal controls and 2.6 times greater than in RVOT ectopy patients.

***VEB fragmentation max***

VEB fragmentation max was greater in definite and incompletely expressed ARVC patients than normal controls and RVOT ectopy patients (7±3, 3±4, 1±3 and 2±3 respectively; table 1; raw data).

VEB fragmentation max was associated with age, not gender or conducted QRS duration (table 2). Adjusted VEB fragmentation max remained greater in ARVC patients than control groups. In incomplete ARVC the odds of VEB fragmentation

max ≥7 (vs <7) was 3.0 times greater than in normal controls and 1.2 times greater than in RVOT ectopy patients.

***Diagnosis of incompletely expressed ARVC using novel VEB indices***

VEQSI max was the strongest VEB index for ARVC diagnosis (AUC 0.993; 95%CI 0.980-0.998; table 3; supplementary figure). Although VEB number, VEQSI max, VEB morphologies and VEB fragmentation max were all univariate markers of disease, following multivariable analysis only VEQSI max remained significant (OR 2.35; 95%CI 1.30-4.25; p=0.005; supplementary table 3). VEQSI max effectively differentiated incompletely expressed ARVC patients from normal controls (41.76; 95%CI 35.51-48.46; p<0.001) and RVOT ectopy patients (33.14; 95% CI 25.73-40.55; p<0.001; table 2). With an optimum threshold of >180ms VEQSI max had 98% sensitivity and specificity for ARVC diagnosis (table 3).

**Comparison with Task Force criteria**

VEQSI max >180ms identified 100% definite ARVC patients whereas major Task Force criteria for arrhythmias were met in 13-23% and minor criteria in 53-73% patients (supplementary table 4). VEQSI max >180ms identified 88% incompletely expressed ARVC patients whereas major Task Force criteria for arrhythmias were met in 10% and minor criteria in 38-45% patients. VEQSI max excluded 85% of RVOT ectopy patients whereas minor ARVC Task Force criteria for arrhythmias were met in 58% patients.

**Prediction of events**

VEQSI max was longer in ARVC patients with previous life-threatening arrhythmia than in those without (217±18ms and 199±11ms; supplementary table 5; raw data). Univariate analysis identified potential markers of prior life-threatening events but after multivariable analysis only unexplained syncope and VEQSI max remained significant (table 4). VEQSI max was the strongest predictor with a 1ms increase in VEQSI max increasing the odds of previous life-threatening arrhythmia by a factor of 1.1 (95%CI 1.03-1.15; p=0.001).

**VEQSI max and RV structural changes**

In patients with normal RV size, VEQSI max was longer in those with definite and incompletely expressed ARVC compared with normal controls and RVOT ectopy patients (202±15ms, 200±12ms, 159±16ms and 165±14ms respectively). In RVOT origin VEB, VEQSI was longer in patients with definite and incompletely expressed ARVC compared with normal controls and RVOT ectopy patients (LBBB inferior axis VEB 184±25ms, 191±18ms, 159±15ms and 161±14ms respectively; figure 3).

**Antiarrhythmic drugs**

Nine ARVC patients received sotalol therapy which can influence conduction. Following exclusion of these patients, VEQSI max remained longer in definite and incompletely expressed ARVC patients compared with normal controls and

RVOT ectopy patients (206±18ms, 200±12ms, 161±15ms and 165±14ms respectively).

## Discussion

VEB indices: VEQSI max, number of VEB morphologies and VEB fragmentation max distinguished patients with definite and incompletely expressed ARVC from normal controls and patients with normal heart RVOT ectopy. VEQSI max was the strongest index. VEQSI max >180ms had high sensitivity and specificity for the identification of ARVC, making it a potentially useful diagnostic test. Moreover VEQSI max >180ms increased the diagnostic yield in ARVC patients compared with Task Force criteria for arrhythmias.

*Diagnosis of incompletely expressed ARVC*

There is no gold standard investigation for ARVC; diagnosis relies on meeting Task Force criteria. First-degree relatives of a proband are frequently referred for screening without signs or symptoms and there is phenotypic heterogeneity.(11–13) Early ARVC may go unrecognized or be confused with RVOT ectopy.

Our incompletely expressed ARVC patients had an affected first-degree relative, one minor Task Force criterion, non-diagnostic cardiac imaging and insufficient phenotype to fulfil definite criteria. These are patients where diagnosis is most challenging. ARVC identification and differentiation from RVOT ectopy is

important to guide therapy and follow-up and assess SCD risk. Whereas RVOT ectopy appears benign, ARVC is associated with risk of SCD.(5,6)

In early ARVC, cardiac imaging is frequently normal and electrical changes appear to predate structural changes.(4,7,8) Despite a perception that innocent ventricular arrhythmia arises in the RVOT, it is common to observe outflow tract arrhythmia in ARVC.(4) Both of these factors can make early diagnosis difficult.

In our incompletely expressed ARVC patients, 100% had normal RV size and function and 35% VEB originated in the RVOT. Major and minor ARVC Task Force arrhythmia criteria were demonstrated in only 10% and 45% of these patients respectively, but VEQSI max >180ms identified 88% as affected. In addition, VEQSI max >180ms was found in only 15% RVOT ectopy patients whereas minor Task Force criteria identified 58% RVOT ectopy patients as potential carriers of ARVC.

Multivariable analysis demonstrated that VEQSI max was a stronger marker for ARVC diagnosis compared with other VEB indices. VEQSI max had the highest sensitivity and specificity and we propose it as the most useful index. Automated measurement of VEQSI max is likely to be most robust and we have shown that Holter monitoring with fewer leads is sufficient.(2)

*Comparison with other studies*

Longer QRS duration in definite ARVC patients compared with RVOT ectopy patients has been demonstrated during VT.(14,15) QRS duration ≥120ms (lead I) from paper ECGs had 88-100% sensitivity and 46-48% specificity for ARVC diagnosis. Addition of other parameters (QRS axis, notching, precordial transition during VT and T-wave inversion in leads V1+V2 on the resting ECG) improved specificity to 100%.(14,15) VEQSI max, however, demonstrates similar sensitivity and specificity as an isolated index and is useful for the diagnosis of incompletely expressed ARVC as well as definite disease.

VEQSI measurement only requires presence of VEB making it applicable for a greater number of patients. In our cohorts 30% definite ARVC, 15% incompletely expressed ARVC and 8% RVOT ectopy patients exhibited VT, whereas 100% definite ARVC and RVOT ectopy patients and 90% incompletely expressed ARVC patients demonstrated VEB. The VEQSI max diagnostic cut-off was longer than QRS duration measured during VT on paper ECGs.(14,15) However, VEQSI max was measured from the earliest VEB onset to the latest termination across all ECG leads whereas in previous studies QRS measurements were made for each individual lead. In addition, digital recording with high magnification measurement of an isolated VEB allows more accurate determination of VEB onset and termination than during VT on paper ECGs where low magnification measurements are more challenging and VEB onset and termination may be obscured by successive beats.

*Risk stratification*

ARVC risk stratification is challenging and SCD is the first presentation in up to 50% of individuals.(5,13) Death frequently occurs during the concealed phase. Aborted SCD, VT causing hemodynamic compromise and unexplained syncope are risk factors for subsequent events and warrant implantable cardioverter-defibrillator therapy. Less well established risk factors include left ventricular involvement and family history of SCD.(16–18) In our ARVC patients, VEQSI max was longer in those with previous life-threatening arrhythmia compared with asymptomatic subjects. Multivariable analysis established that unexplained syncope and VEQSI max were independent markers of prior life-threatening events and VEQSI max was the strongest. VEQSI max may be a predictor of arrhythmic events, but prospective follow-up with survival analysis is necessary to confirm this.

*VEQSI max*

Ventricular arrhythmias arising near the septum have shorter QRS duration than those arising in the free wall due to more proximal activation of the His-Purkinje system and simultaneous LV/RV activation.(19) Longer VEQSI max in ARVC patients could result from VEB originating in the RV free wall, causing lengthening of the conduction pathway compared with VEB arising near the septum in normal controls and RVOT ectopy patients. However, when RVOT origin VEB were considered in isolation, VEQSI max remained longer in ARVC

patients than controls. In addition when patients with RV dilatation were excluded, VEQSI max remained longer in ARVC patients compared with controls. Myocardial VEB velocity appears slower in ARVC even in the absence of overt structural anomalies. Indeed invasive electrophysiological mapping of genetically proven ARVC patients without overt structural disease demonstrated conduction slowing compared with controls.(7) This was supported by histopathological mis-localisation of gap junction proteins. In addition, in idiopathic ventricular arrhythmia patients, broader QRS duration has been associated with myocardial scar.(20)

**Conclusion**

VEQSI max, number of VEB morphologies and VEB fragmentation max distinguish ARVC patients, including those with incomplete disease expression, from healthy controls and RVOT ectopy patients. VEQSI max is the strongest diagnostic marker. We propose VEQSI max as a promising clinical index for ARVC diagnosis and risk stratification.

**Study Limitations**

ARVC is a rare disease and the sample size is relatively small. In rare diseases sensitivity and specificity tests result in high values and ROC curve analysis has lower accuracy. The interpretation of results should be considered in this context. Prospective validation of these phenotyping parameters was not possible which represents a major study limitation.

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**References**

1. Bastiaenen R, Batchvarov V, Gallagher MM. Ventricular automaticity as a predictor of sudden death in ischaemic heart disease. Europace 2012;14(6):795–803.

2. Gallagher MM, Padula M, Sgueglia M, Santini L, Voci P, Mahon NG, Yap YG, Romeo F. Electrocardiographic markers of structural heart disease and predictors of death in 2332 unselected patients undergoing outpatient Holter recording. Europace 2007;9(12):1203–1208.

3. Moulton KP, Medcalf T, Lazzara R. Premature ventricular complex morphology. A marker for left ventricular structure and function. Circulation 1990;81(4):1245–1251.

4. Marcus FI, McKenna WJ, Sherrill D et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia. Eur Heart J 2010;31(7):806-814.

5. Dalal D, Nasir K, Bomma C, et al. Arrhythmogenic Right Ventricular Dysplasia: A United States Experience. Circulation 2005;112(25):3823–3832.

6. Lemery R, Brugada P, Bella PD, Dugernier T, van den Dool A, Wellens H. Nonischemic ventricular tachycardia. Clinical course and long-term follow-up in patients without clinically overt heart disease. Circulation 1989;79(5):990–999.

7. Gomes J, Finlay M, Ahmed AK et al. Electrophysiological abnormalities precede overt structural changes in arrhythmogenic right ventricular cardiomyopathy due to mutations in desmoplakin-A combined murine and human study. Eur Heart J 2012;33(15):1942–1953.

8. Quarta G, Ward D, Tomé Esteban MT, Pantazis A, Elliott PM, Volpe M, Autore C, McKenna WJ. Dynamic electrocardiographic changes in patients with arrhythmogenic right ventricular cardiomyopathy. Heart 2010;96(7):516–522.

9. Miller JM, Marchlinski FE, Buxton AE, Josephson ME. Relationship between the 12-lead electrocardiogram during ventricular tachycardia and endocardial site of origin in patients with coronary artery disease. Circulation 1988;77(4):759–766.

10. Das MK, Suradi H, Maskoun W, Michael MA, Shen C, Peng J, Dandamudi G, Mahenthiran J. Fragmented Wide QRS on a 12-Lead ECG: A Sign of Myocardial Scar and Poor Prognosis. Circ Arrhythmia Electrophysiol 2008;1(4):258–268.

11. Behr ER, Dalageorgou C, Christiansen M, Syrris P, Hughes S, Tomé Esteban MT, Rowland E, Jeffrey S, McKenna WJ. Sudden arrhythmic death syndrome: familial evaluation identifies inheritable heart disease in the majority of families. Eur Heart J 2008;29(13):1670–1680.

12. Hamid MS, Norman M, Quraishi A, Firoozi S, Thaman R, Gimeno JR, Sachdev B, Rowland E, Elliott PM, McKenna WJ. Prospective evaluation of relatives for familial arrhythmogenic right ventricular cardiomyopathy/dysplasia reveals a need to broaden diagnostic criteria. J Am Coll Cardiol 2002;40(8):1445–1450.

13. Quarta G, Muir A, Pantazis A, Syrris P, Gehmlich K, Garcia-Pavia P, Ward D, Sen-Chowdhry S, Elliott PM, McKenna WJ. Familial Evaluation in Arrhythmogenic Right Ventricular Cardiomyopathy: Impact of Genetics and Revised Task Force Criteria. Circulation 2011;123(23):2701–2709.

14. Hoffmayer KS, Machado ON, Marcus GM et al. Electrocardiographic comparison of ventricular arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy and right ventricular outflow tract tachycardia. J Am Coll Cardiol 201;58(8):831–8.

15. Ainsworth CD, Skanes AC, Klein GJ, Gula LJ, Yee R, Krahn AD. Differentiating arrhythmogenic right ventricular cardiomyopathy from right ventricular outflow tract ventricular tachycardia using multilead QRS duration and axis. Heart Rhythm 2006;3(4):416–23.

16. Corrado D, Calkins H, Link MS et al. Prophylactic Implantable Defibrillator in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia and No Prior Ventricular Fibrillation or Sustained Ventricular Tachycardia. Circulation 2010;122(12):1144–1152.

17. Garratt CJ, Elliott P, Behr E et al. Heart Rhythm UK position statement on clinical indications for implantable cardioverter defibrillators in adult patients with familial sudden cardiac death syndromes. Europace 2010;12(8):1156–1175.

18. Corrado D, Leoni L, Link MS et al. Implantable Cardioverter-Defibrillator Therapy for Prevention of Sudden Death in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia. Circulation 2003;108(25):3084–3091.

19. Josephson ME, Callans DJ. Using the twelve-lead electrocardiogram to localize the site of origin of ventricular tachycardia. Heart Rhythm 2005;2(4):443–6.

20. Wijnmaalen AP, Stevenson WG, Schalij MJ, Field ME, Stephenson K, Tedrow UB, Koplan BA, Putter H, Epstein LM, Zeppenfeld K. ECG Identification of Scar-Related Ventricular Tachycardia With a Left Bundle-Branch Block Configuration. Circ Arrhythmia Electrophysiol 2011;4(4):486–493.

## Tables

Table 1 Data from normal controls, right ventricular outflow tract (RVOT) ectopy patients and patients with definite and incompletely expressed arrhythmogenic right ventricular cardiomyopathy (ARVC).

| | Definite ARVC (n=30) | Normal controls (n=116) | Normal heart RVOT ectopy (n=26) | Incompletely expressed ARVC (n=40) |
|---|---|---|---|---|
| Age (years) | 47±12 | 40±15 | 46±17 | 44±18 |
| Gender (male;%) | 60 | 56 | 27 | 43 |
| Medications (%) | | | | |
| • Beta-blocker | 70 | 0 | 27 | 25 |
| • Sotalol | 20 | 0 | 0 | 8 |
| • Other | 20 | 0 | 19 | 0 |
| Pathogenic mutation (%) | 47 | NA | NA | 55 |
| Right ventricular dilatation (%) | | | | |
| • Normal | 47 | 100 | 100 | 100 |
| • Mild | 37 | 0 | 0 | 0 |
| • Moderate/severe | 17 | 0 | 0 | 0 |
| Right ventricular impairment (%) | | | | |
| • Normal | 50 | 100 | 100 | 100 |
| • Mild | 33 | 0 | 0 | 0 |
| • Moderate/severe | 17 | 0 | 0 | 0 |
| Left ventricular involvement (%) | 23 | 0 | 0 | 13 |
| T-wave inversion V1+V2 (%) | 70 | 1 | 12 | 8 |
| T-wave inversion beyond V2 (%) | 57 | 0 | 0 | 0 |
| Epsilon wave (%) | 10 | 0 | 0 | 0 |
| Abnormal SAECG (%) | 58 | NA | NA | 48 |
| Prior frequent VEB>500/24 hours (%) | 33 | NA | NA | 43 |
| Prior VT LBBB superior axis (%) | 23 | NA | NA | 0 |
| Prior VT LBBB other axis (%) | 57 | NA | NA | 3 |
| Subjects with VEB (%) | 100 | 57 | 100 | 90 |
| VEB/24 hours (n;median±IQR) | 416±1423 | 3±8 | 1003±3877 | 267±1083 |
| VEB morphology (%) | | | | |
| • LBBB superior | 41 | 32 | 21 | 36 |
| • LBBB inferior | 31 | 25 | 61 | 35 |
| • RBBB superior | 23 | 36 | 14 | 21 |
| • RBBB inferior | 5 | 7 | 4 | 8 |
| Frequent VEB>500/24 hours (%) | 47 | 1 | 54 | 38 |
| Subjects with VT (%) | 30 | 0 | 8 | 15 |
| VT LBBB superior axis (%) | 13 | 0 | 0 | 10 |
| VT other axis (%) | 17 | 0 | 8 | 5 |
| VEQSI max (ms;mean±SD) | 209±18 | 159±16 | 165±14 | 200±12 |
| VEB morphologies (n;median±IQR) | 5±4 | 1±1 | 2±1 | 3±4 |
| VEB fragmentation max (n;median±IQR) | 7±3 | 1±3 | 1±3 | 3±4 |

VEB, ventricular ectopic beat; VT, ventricular tachycardia; VEQSI, ventricular ectopic QRS interval

Table 2 Univariate and multivariable analyses of the ventricular ectopic beat (VEB) indices adjusted for age, gender and conducted QRS duration.

| | Univariate analysis | | | Final model | | |
|---|---|---|---|---|---|---|
| VEQSI max | Estimate | p-value | 95%CI | Estimate | p-value | 95%CI |
| Age (5-year effect) | 1.37 | 0.038 | 0.02,0.53 | 1.91 | 0.001 | 0.80,3.03 |
| Gender | -6.90 | -.102 | -15.18,1.38 | -7.97 | 0.001 | -12.77,-3.16 |
| Conducted QRS | 0.35 | 0.019 | 0.06,0.64 | | | |
| **D-ARVC vs. NC†** | 49.93 | <0.0001 | 43.28,56.59 | **49.05** | **<0.001** | **42.70,55.40** |
| **D-ARVC vs. RVOT*** | | | | **40.43** | **<0.001** | **32.56,48.29** |
| **IE-ARVC vs. NC†** | 40.89 | <0.0001 | 34.62,47.15 | **41.76** | **<0.001** | **35.51,48.46** |
| **IE-ARVC vs. RVOT*** | | | | **33.14** | **<0.001** | **25.73,40.55** |
| VEB morphologies | OR | p-value | 95%CI | OR | p-value | 95%CI |
| Age (5-year effect) | 1.19 | 0.001 | 1.07,1.33 | 1.26 | <0.001 | 1.11,1.44 |
| Gender | 0.52 | 0.049 | 0.27,0.99 | 0.42 | 0.039 | 0.18,0.96 |
| Conducted QRS | 1.02 | 0.006 | 0.99,1.05 | | | |
| **D-ARVC vs. NC** | 26.00 | <0.001 | 9.16,73.82 | **31.4** | **<0.001** | **10.27,96.07** |
| **D-ARVC vs. RVOT** | 3.48 | <0.001 | 2.05,4.90 | **3.67** | **<0.001** | **2.15,5.20** |
| **IE-ARVC vs. NC** | 7.84 | <0.001 | 3.03,20.27 | **11.13** | **<0.001** | **3.93,31.55** |
| **IE-ARVC vs. RVOT** | 2.28 | 0.001 | 0.92,3.64 | **2.63** | **<0.001** | **1.16,4.10** |
| VEB fragmentation max | OR | p-value | 95%CI | OR | p-value | 95%CI |
| Age (5-year effect) | 1.03 | 0.001 | 1.01,1.05 | 1.22 | <0.001 | 1.10,1.36 |
| Gender | 0.51 | 0.032 | 0.28,0.94 | | | |
| Conducted QRS | 1.03 | 0.024 | 1.00,1.04 | | | |
| **D-ARVC vs. NC** | 27.95 | <0.001 | 10.57,73.93 | **30.37** | **<0.0001** | **11.24,82.07** |
| **D-ARVC vs. RVOT** | 3.31 | <0.001 | 2.15,4.46 | **3.5** | **<0.0001** | **2.30,4.70** |
| **IE-ARVC vs. NC** | 2.72 | <0.015 | 1.22,6.08 | **2.98** | **<0.0001** | **1.30,6.84** |
| **IE-ARVC vs. RVOT** | 0.97 | 0.061 | -0.05,1.99 | **1.19** | **0.028** | **0.13,2.26** |

†Final model with NC as baseline cohort

*Final model with RVOT ectopy as baseline cohort

D-ARVC, definite arrhythmogenic right ventricular cardiomyopathy; IE-ARVC, incompletely expressed ARVC; NC, normal controls; RVOT, right ventricular outflow tract ectopy; VEQSI, ventricular ectopic QRS interval; OR, odds ratio; CI, confidence interval

Table 3 Sensitivity and specificity of the ventricular ectopic beat (VEB) indices in arrhythmogenic right ventricular cardiomyopathy diagnosis.

| | AUC | 95%CI | AUC difference | AUC difference | 95%CI | p-value | Threshold | Sensitivity | Specificity |
|---|---|---|---|---|---|---|---|---|---|
| VEQSI max(ms) | 0.993 | (0.980,0.998) | - | - | - | - | 180 | 0.98 | 0.98 |
| VEB morphologies(n) | 0.845 | (0.772,0.908) | VEQSI max vs. VEB morphologies | -0.148 | (-0.219,-0.088) | <0.0001 | 2 | 0.76 | 0.75 |
| VEB fragmentation max(n) | 0.819 | (0.739,0.879) | VEQSI max vs. VEB fragmentation max | -0.174 | (-0.249,-0.112) | <0.0001 | 2 | 0.71 | 0.71 |
| | | | VEB morphologies vs. VEB fragmentation max | -0.026 | (-0.087,0.025) | 0.37 | | | |

VEQSI, ventricular ectopic QRS interval; AUC, area under the curve; CI, confidence interval

Table 4 Univariate and multivariable analyses of markers for prior life-threatening arrhythmia in arrhythmogenic right ventricular cardiomyopathy patients.

| | Univariate Analysis | | | Multivariable Analysis | | |
|---|---|---|---|---|---|---|
| Variable | OR | p-value | 95%CI | OR | p-value | 95%CI |
| Age | 1.02 | 0.352 | 0.98-1.05 | | | |
| Gender | **0.23** | **0.022** | **0.07-0.81** | | | |
| Family history of sudden death | **0.23** | **0.022** | **0.07-0.81** | | | |
| Left ventricular involvement | 2.50 | 0.172 | 0.67-9.31 | | | |
| VT on Holter | 1.63 | 0.448 | 0.46-5.69 | | | |
| Unexplained syncope | **12.82** | **0.004** | **2.27-72.28** | **12.60** | **0.015** | **1.63-97.35** |
| VEQSI max (1ms increment) | **1.09** | **0.001** | **1.04-1.15** | **1.09** | **0.001** | **1.03-1.15** |
| VEQSI max (5ms increment) | | | | **1.53** | **0.001** | **1.19-1.98** |
| VEQSI max (10ms increment) | | | | **2.35** | **0.001** | **1.41-3.92** |
| Constant | | | | 0.18 | 0.000 | 0.08-0.40 |

OR, odds ratio; CI, confidence interval; VT, ventricular tachycardia; VEQSI, ventricular ectopic QRS interval

## Figure Legends

Figure 1

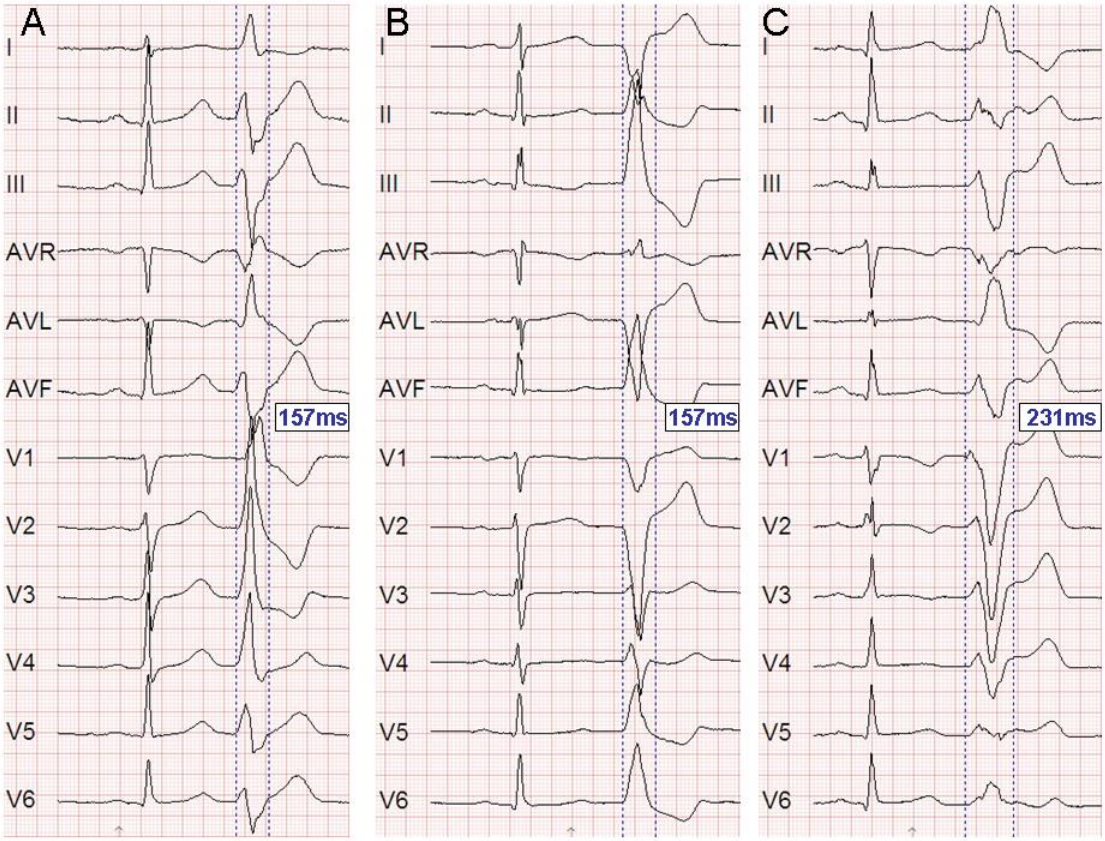
Measurement of the ventricular ectopic QRS interval (VEQSI). Panel A demonstrates a narrow ventricular ectopic beat (VEB) from a healthy control (VEQSI 157ms). Panel B demonstrates a narrow right ventricular outflow tract VEB from a patient with a structurally normal heart (VEQSI 157ms). Panel C demonstrates a broad VEB from a patient with arrhythmogenic right ventricular cardiomyopathy (VEQSI 231ms).

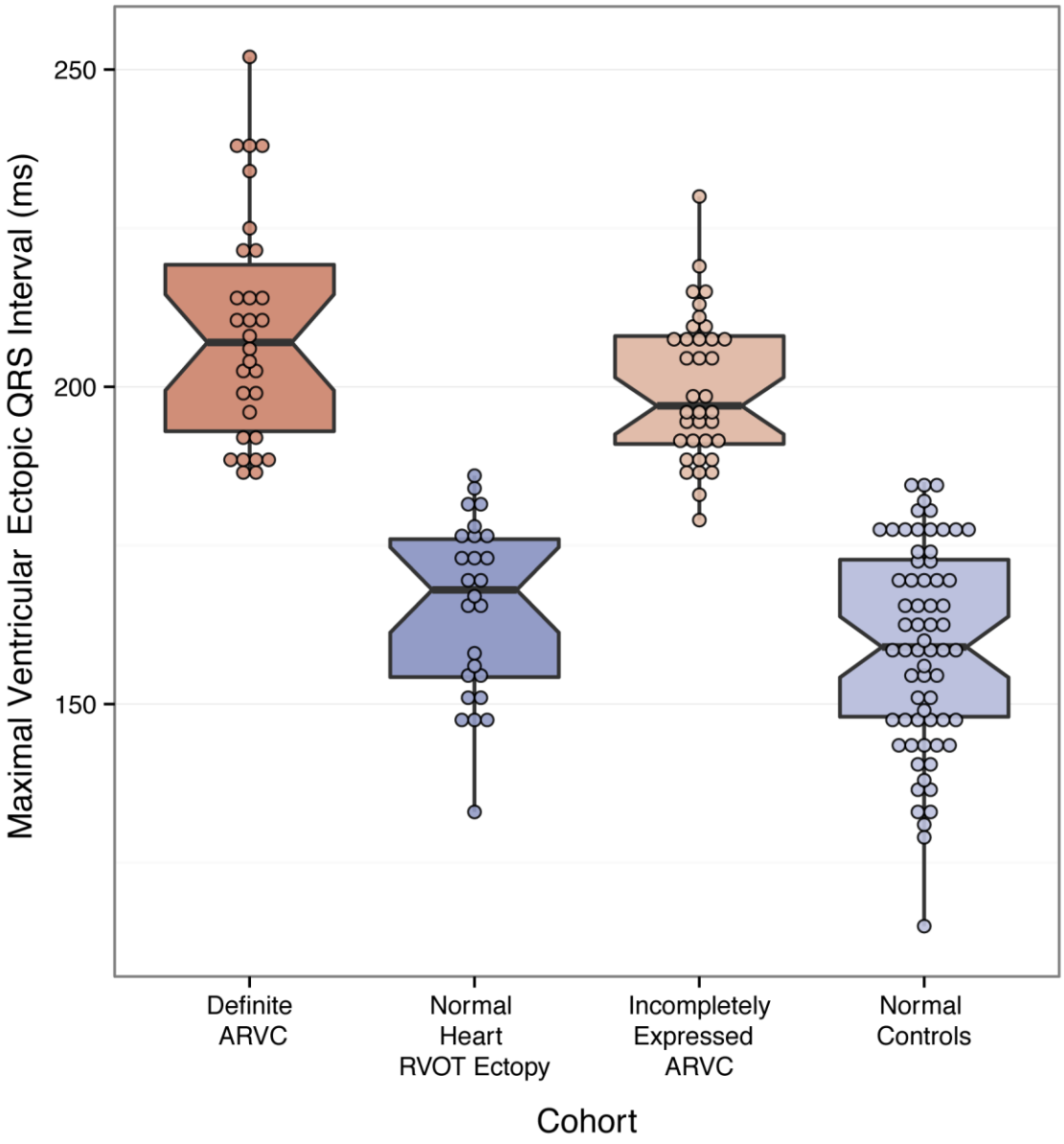
Figure 2

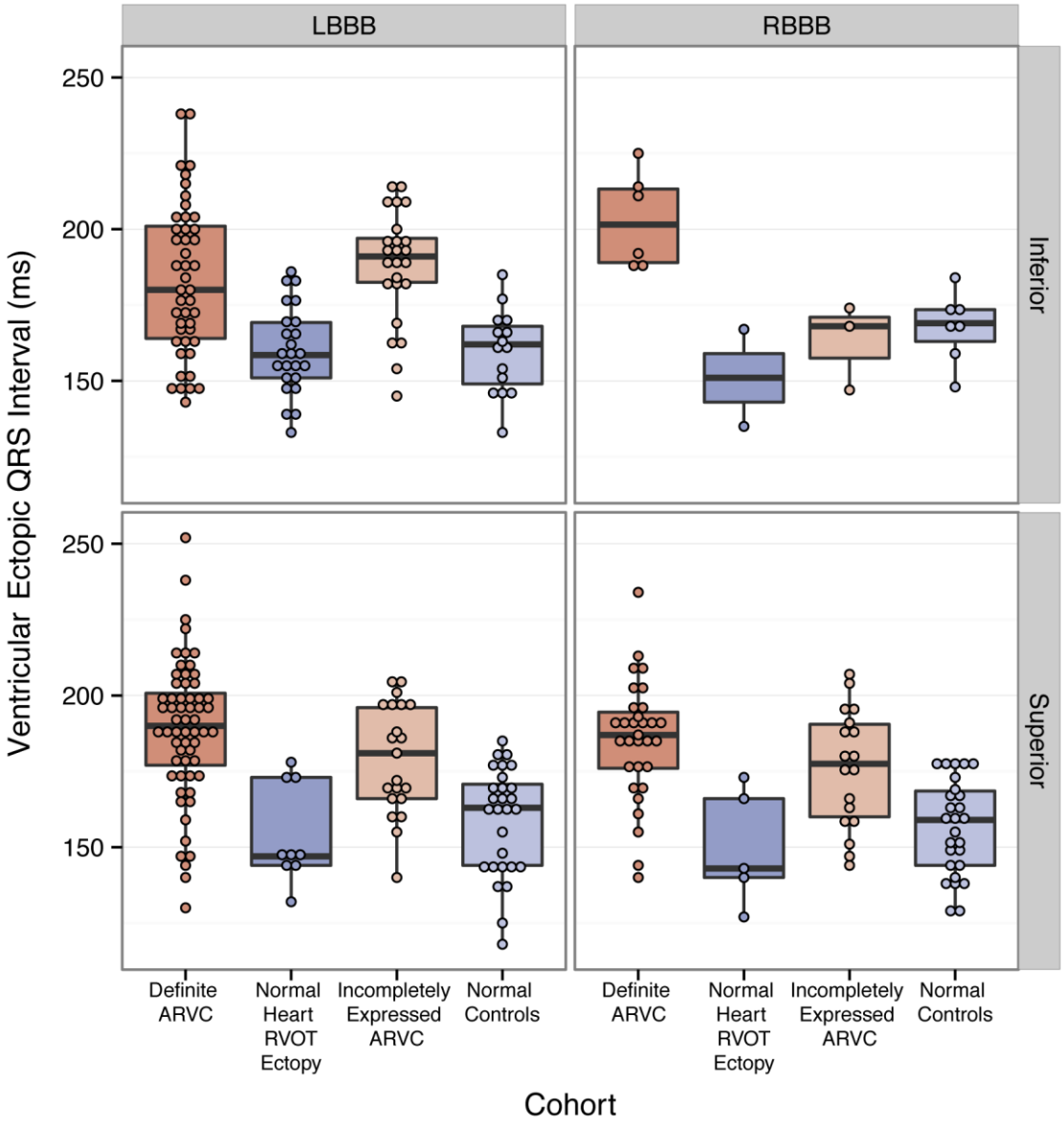
The maximal ventricular ectopic QRS interval (VEQSI max) in normal controls, patients with definite and incompletely expressed arrhythmogenic right ventricular cardiomyopathy (ARVC) and patients with normal heart right ventricular outflow tract (RVOT) ectopy (raw data).

Figure 3

The ventricular ectopic QRS interval (VEQSI) in normal controls, patients with definite and incompletely expressed arrhythmogenic right ventricular cardiomyopathy (ARVC) and patients with normal heart right ventricular outflow tract (RVOT) ectopy according to ventricular ectopic beat (VEB) morphology (raw data).


A
I
II
III
AVR
AVL
AVF
V1
V2
V3
V4
V5
V6
157ms
B
I
II
III
AVR
AVL
AVF
V1
V2
V3
V4
V5
V6
157ms
C
I
II
III
AVR
AVL
AVF
V1
V2
V3
V4
V5
V6
231ms


Maximal Ventricular Ectopic QRS Interval (ms)
250
200
150
Definite ARVC
Normal Heart RVOT Ectopy
Incompletely Expressed ARVC
Normal Controls
Cohort


LBBB
RBBB
Inferior
Superior
Ventricular Ectopic QRS Interval (ms)
250
200
150
Definite ARVC
Normal Heart RVOT Ectopy
Incompletely Expressed ARVC
Normal Controls
Cohort