Non-invasive detection of exercise induced cardiac conduction abnormalities in SCD survivors in the Inherited Cardiac Conditions

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Abstract

Aim:

Rate adaptation of the action potential ensures spatial heterogeneities in conduction across the myocardium are minimised at different heart rates providing a protective mechanism against ventricular fibrillation (VF) and sudden cardiac death (SCD), which can be quantified by the Ventricular Conduction Stability (V-CoS) test previously described. We tested the hypothesis that patients with a history of aborted SCD due to an underlying channelopathy or cardiomyopathy have a reduced capacity to maintain uniform activation following exercise.

Methods

60 individuals, with (n=28) and without (n=32) previous aborted-SCD event underwent ECGi recordings following exercise treadmill test. These included 25 Brugada Syndrome, 13 Hypertrophic Cardiomyopathy, 12 idiopathic VF and 10 healthy controls. Data was inputted into the V-CoS programme to calculate a V-CoS score that indicate the percentage of ventricle that showed no significant change in ventricular activation, with a lower score indicating the development of greater conduction heterogeneity.

Results:

The SCD group, compared to those without, had a lower median (interquartile range) V-CoS score at peak exertion (92.8%(89.8-96.3%) vs 97.3%(94.9-99.1%); $p<0.01$) and 2 minutes into recovery (95.2%(91.1-97.2%) vs (98.9%(96.9-99.5%); $p<0.01$). No significant difference was observable later into recovery at 5 or 10 minutes. Using the lowest median V-CoS scores obtained during the entire recovery period post exertion, SCD survivors had a significantly lower score than those without for each of the different underlying aetiologies.

Conclusion:

Data from this pilot study demonstrate the potential use of this technique in risk stratification for the inherited cardiac conditions.

Keywords: Sudden cardiac death, V-CoS, ECGi, Risk Stratification, idiopathic ventricular fibrillation, Brugada Syndrome, Hypertrophic Cardiomyopathy

Condensed abstract

We assess a novel method to rapidly quantify the degree of conduction heterogeneity that may develop in those with an impaired rate adaptive response. Data from this pilot study demonstrate the potential use of this technique in risk stratification for the inherited cardiac conditions regardless of underlying cause

What's new

- Survivors of aborted sudden cardiac arrest develop greater spatial heterogeneities in conduction and repolarisation than those without following modulation in autonomic tone and heart rate.
- We assess the V-CoS test in its ability to discriminate between individual at high risk and low risk of future ventricular arrhythmias in a range of of Inherited Cardiac Conditions
- The V-CoS test detects abnormalities in cardiac conduction following exercise and has the potential to improve on current risk stratification techniques in the Inherited Cardiac Conditions.

Introduction

Arrhythmogenicity in the inherited cardiac conditions (ICCs) begins with the inheritance or spontaneous acquisition of one or several genetic mutations. These consequentially translate into channelopathies or cardiomyopathies that impair the propagation and physiological rate adaptive responses of the action potential, affecting the recovery of excitability across the ventricles which predict ventricular fibrillation. [1-4] This may be further modulated by heart rate or changes in autonomic tone which have previously been observed to play a critical role in the development of arrhythmias in the ICCs. [5-8]

We developed and described the V-CoS test previously as a method to quantify the alterations in whole heart activation patterns following exercise in-vivo.[9] We previously demonstrated the utility of this test as a potential marker of risk, although it remained unclear if this could be applied as an adjunctive discriminator for the different ICCs and those with an idiopathic cause of VF. In this study, we validate the V-CoS test in a larger cohort of patients with different ICCs and test the hypothesis that SCD survivors, irrespective of the underlying genetic abnormality, have an abnormal rate adaptive response resulting in greater spatial heterogeneities in conduction developing following exertion than those without a previous history of aborted SCD.

Methods

Study population

For this study, patients with and without a previous aborted sudden cardiac death (SCD) or equivalent event with different ICCs were recruited. Patients meeting criteria for a diagnosis of Brugada Syndrome (BrS), Hypertrophic Cardiomyopathy (HCM) or an idiopathic cause

ventricular fibrillation/tachycardia (iVF/VT) were identified and enrolled.[7] Patients with structurally normal hearts with no history of syncope or family history of sudden death/ICC undergoing electrophysiological studies and required ECGi mapping for ventricular ectopy or supra-ventricular arrhythmias were also studied as a control group. Individuals with an aborted SCD or equivalent event were defined as those requiring resuscitation following a cardiac arrest or an appropriate shock from their ICD.

Study protocol

Enrolled patients had the non-invasive electro-cardiographic imaging (ECGi) vest fitted and secured, before undergoing exercise treadmill and a non-contrast CT chest on the same day. The Bruce protocol was employed and stopped when maximal exertion was achieved. This was defined as reaching and sustaining maximum target heart rate adjusted for age, or cessation owing to fatigue after achieving a minimum of 85% of their maximum target heart rate. Patients were immediately returned to the supine position where ECGi recordings were then performed over a 10 minute recovery period, to eliminate interference, movement and motion artefact. Subjects were excluded from analysis if they were unable to perform or complete exercise treadmill test protocol on the day of ECGi recording. The study protocol was reviewed and approved by the National Research Ethics Committee - London (ref:14/LO/1318).

The body surface electrogram and reconstructed unipolar epicardial electrogram (EGM) signal data obtained over this period was subsequently extracted from the ECGi system and analysed with the V-CoS programme **(Figure 1)**. The torso, ventricles, tricuspid and mitral valve and left anterior descending artery geometry were also segmented from the cardiac CT

scan using the EcVUE user interface within the ECGi system software. Data encoding the torso and ventricular shell, valves and coronary arteries was also extracted and processed with the V-CoS programme.

ECGI and Signal Processing with the V-CoS test

The EcVUE system (Medtronic Inc, USA) was used for ECGi processing. This involved body surface potential data obtained via a 252-electrode vest which was combined with patient specific heart-torso geometry derived from a thoracic CT scan (**Figure 1 & Supplemental Figure 1**). Using inverse solution mathematical algorithms, the ECGi system reconstructed epicardial unipolar electrograms and panoramic activation maps over a single sinus beat which were visualised on a digitised image of the patient's heart on EcVUE system user interface.

The V-CoS programme has been described in detail previously. [9] Briefly, the programme allows the rapid and automated comparison of ventricular electrogram data and activation patterns between two different beats – one from a reference phase (e.g. resting baseline) and the other from a test phase (e.g. peak exertion). Differences in local activation timings between the two phases were calculated for every electrogram with a spatial point over the heart surface or mesh created by the ECGi system (fuller description under supplementary methods).

To provide a measure of conduction stability, or a surrogate measure of an appropriate rate adaptive response, a V-CoS score was automatically derived. This indicated the percentage of

epicardial electrograms across the ventricular surface where no significant changes in local activation timing (less than 10ms) occurred between the reference and test phases. A higher percentage or score denoted greater conduction stability or a normal rate adaptive mechanism. Examples of reconstructed ECGi activation and V-CoS maps for each sub-group of study patients are shown in **supplemental figure 2**.

Data analysis

Electrograms were analysed at peak exertion (defined as within a minute of cessation of exercise), and during recovery at 2 minutes, 5 minutes and 10 minutes. Calculation of V-CoS scores were determined with reference to the end of the 10-minute recovery period and were based on detecting differences or changes in local activation timing (LAT) at each point on the ventricular surface that was in excess of 10 milliseconds as previously described.

Receiver Operating Characteristic (ROC) analysis and graphs were calculated to assess the diagnostic performance of the V-CoS test, with the area under the curve expressed as the C-statistic. This was based on the minimum V-CoS score achieved by each individual at all test phases. The Youden index, defined as *sensitivity+specificity-1.00,* was then calculated for all points on the ROC curve.[10] The maximum value of the index was used as the criterion for selecting a cut-off point or threshold to denote optimal sensitivity and specificity.

Assessment of SCD risk with conventional risk stratification techniques

In patients with BrS, a prior history of syncope and the presence of a spontaneous Type I BrS pattern as defined previously was ascertained at enrolment[16], or before the SCD event in

survivors to ascertain the predictive value of these risk markers. Individuals were then grouped into three categories according to the presence these factors. High risk – denoting the presence of both syncope and spontaneous type I pattern; Intermediate risk – the presence of either syncope or spontaneous type I pattern; Low risk – the absence of either.

For patients with HCM, the ESC 5 year SCD risk score was calculated for each individual.[11] This was performed retrospectively in study patients 16 years or older based on data obtained on initial evaluation. To assess the ESC risk score's predictive value in those who first presented with an aborted SCD event to our institute, a prior history of syncope was considered present if occurred before their presenting SCD event. All other clinical parameters were obtained based on subsequent work up. High risk individuals were deemed as those having a 5 year risk of >6%; Intermediate risk – 4 to 6%; Low risk - <4%.[12]

Statistical analysis

Normality testing was performed using the D'Agostino-Pearson test. For non-normally distributed variables, the Kruskal-Wallis test (or Friedman's test for repeated measures) was used for comparison of three of more groups. For post hoc analysis, the Mann-Whitney test was employed for comparison between two groups with Dunn's correction where multiple comparisons were required. Statistical analysis was performed using GraphPad PRISM v5 (Graphpad Software Inc, USA), and a p value of <0.05 was considered significant.

Results

Study group characteristics

The V-CoS test was applied to 28 patients with a previously aborted SCD event (mean age 40±11 years, 24 males) and 32 patients without a previous SCD event (mean age 44±12 years, 21 males) who underwent exercise treadmill testing with the ECGi vest. The SCD group comprised of 12 patients with an idiopathic cause of sustained VF/VT, 10 with BrS and 6 with HCM. In the non-SCD group, 15 BrS patients, 7 HCM patients and 10 control patients with structurally normal hearts. A summary of clinical characteristics of these different subgroups are summarised in **supplemental tables 1-4**. In 3 patients (with previous aborted SCD), anti-arrhythmic therapy was not discontinued prior to the study protocol for clinical reasons.

SCD vs non-SCD group

Following peak exertion in both groups, a gradual increase in V-CoS scores (median (interquartile range)) could be observed over the 10 minute recovery period (NSCD group: 97.3% (94.9-99.1%) to 99.8% (99.1-100%), $p<0.001$; SCD group: 92.8% (89.8-96.3%) to 99.8% (98.7-100%), $p<0.001$) (**Figure 2**). In the early recovery period, V-CoS scores were observed to be significantly lower in the SCD than non-SCD group immediately following peak exertion (92.8% (89.8-96.3%) vs 97.3% (94.9-99.1%), $p=0.03$) and at 2 minutes (95.2% (91.1-97.2%) vs 98.9% (96.9-99.5%), $p<0.01$). No significant differences between the groups could be observed by 5 minutes and 10 minutes into recovery (**Table 1**). There were no significant differences in heart rate between groups at each stage of recovery (**Table 1**).

V-CoS scoring within the different subgroups

Sub-group analysis was also performed between SCD and non-SCD patients according to underlying aetiology. A similar pattern of recovery of V-CoS scores in SCD and non-SCD

patients could be observed in all three subgroups:- i) iVF/VT vs controls ii) BrS-SCD vs BrS iii) HCM-SCD vs HCM (**Figure 3 & Supplemental Figure 3**).

Those with previous aborted SCD events were found to have a lower V-CoS score than non-SCD patients in the early stages of recovery for all three subgroups. In the first subgroup, iVF/VT survivors had lower median scores than controls following peak exertion (94.2% vs 96.8%, p=0.06) with a significant difference on recovery at 2 minutes (96.3% vs 98.8%, p=0.006). No significant differences were observed at 5 and 10 minutes. In the BrS group, a significant difference between SCD and non-SCD patients was also observed immediately following peak exertion (92.3% vs 95.1%, p=0.009) and at 2 minutes post-recovery (91.3% vs 97.8%, p=0.001) but not at the other stages. In the HCM group, a significant difference between the SCD and non-SCD patients was only observed following peak exertion (93.4% vs 99.3, p=0.0047).

As the time point during recovery at which conduction abnormalities occurred could have varied for the different ICCs and between individuals, we analysed the lowest V-CoS scores obtained throughout the whole recovery period for each person and pooled their scores according to their sub-groups (**Figure 4 & Supplemental Figure 4**). The median minimal V-CoS scores post exertion were found to be significantly lower in patients with a previously aborted SCD event than those without for all three subgroups (iVF vs controls: 94.2% vs 96.5%, p=0.03) (BrS SCD vs BrS: 90.9% vs 94.5%, p=0.004) (HCM SCD vs HCM: 93.4% vs 99.2%, p=0.004). Although the differences were statistically significant, it was observed that there was a degree of overlap between the iVF subjects and controls (**supplemental**

figure 4), highlighting the likely heterogeneity in the electrophysiological substrate of the iVF group.

Predictive performance of V-CoS and comparison to current risk stratification

Area under the ROC curve (C-statistic) was 0.82 (standard error ±0.05) when applied to all patients in this study. The C-statistic ranged from 0.79-0.93 when it was applied to each of the different subgroups as shown in **Figure 5**. Based on the Youden index, a cut-off minimum V-CoS score at 93.9% provided a sensitivity and specificity of 87.5% and 67.9% respectively when applied to all patients. In the BrS group, a cut off minimum score at 92.3% derived from Youden index, provided a sensitivity and specificity of 80.0% and 86.7% respectively. In HCM, a threshold at 97.0% provided a sensitivity and specificity at 100% and 85.7% respectively. A Youden index derived threshold of 96.4% in iVF/VT provided a sensitivity and specificity of 83.3% and 70.0% respectively.

As an exploratory study of the small subgroups of BrS and HCM patients, V-CoS testing was compared to conventional markers or risk. In the BrS cohort, conventional risk stratification based on the presence of a spontaneous Type I BrS pattern and syncope identified 2 out of 10 (20%) of the patients with aborted SCD events as high risk. Most of these patients would have been identified as low risk given the absence of these parameters. With V-CoS testing, a threshold of 92.3% identified 80% of the SCD cohort as high risk **(Figure 6)**. In the HCM sub-group, the C-statistic for the V-CoS test (0.95) was 0.14 higher than C-statistic of the ESC risk score calculator (0.81). Using the threshold of 97%, the V-CoS test correctly classified 12 out of the 13 patients **(Figure 7)**.

Discussion

In this study, the V-CoS test was applied to a larger cohort of patients with ICC with previous aborted SCD events, who demonstrated a significantly lower V-CoS score than those without SCD events following an exertional stress test. Interestingly, the same pattern was observed for each of the different inherited cardiac condition subgroups enrolled in this study. This supports the hypothesis that increased spatial changes in activation between phases is associated with increased arrhythmogenic potential regardless of the underlying aetiology.

Previous clinical studies in BrS and HCM patients have demonstrated the existence of spatial heterogeneities in conduction [13-15], and increase in arrhythmogenic potential following exertion.[8,16-19] In iVF patients, Peeters and colleagues had previously described the finding of late potentials on SAECG in such a cohort, suggesting the presence of regions with slow conduction to support re-entrant arrhythmias.[20] Saumarez et al had also found that local electrograms were wider and more fractionated after pacing at shorter coupling intervals in patients with iVF when compared to unaffected controls, suggesting that intraventricular conduction delay has a role in the arrhythmogenic mechanism in these patients.[4] Whether the development of spatial heterogeneities in conduction are related purely to the effects of heart rate and/or autonomic modulation is currently unclear and will require further investigation.

A degree of similarity or V-CoS score overlap could also be observed between the controls and BrS/HCM individuals without previous aborted SCD events (**supplemental figures 3 and 4**). This would be in keeping with the notion that absence of significant conduction delay or the development of spatial heterogeneities in conduction would be at lower risk of developing re-entrant ventricular arrhythmias even in the presence of an inherited cardiac

condition. It was of interest to observe that individuals with HCM (without previous aborted SCD) had similar and overlapping scores to low risk individuals without structural heart disease. We postulate that this may relate to the degree of underlying fibrosis present and its correlation with VCoS scores will require further investigation.

As a measure of arrhythmogenic potential, the minimum V-CoS score was considered as the pattern of V-CoS recovery appeared to differ between groups. In the iVF and HCM groups the lowest V-CoS scores could be primarily observed just after peak exertion in comparison to that seen in the BrS group where a lowered V-CoS score could be observed at 2 minutes in recovery. This variation in arrhythmogenic potential is in keeping with clinical conservation and reports of ventricular arrhythmias occurring during peak exertion rather than recovery in HCM, and on early recovery of post exertion in BrS.[16,17,19]

Based on the Youden's index employed in the analysis of the ROC curves, there appeared to be different thresholds or cut-offs to indicate the optimal sensitivity and specificity of the V-CoS test. Whilst the interpretation of this is limited by the relatively small numbers in each group, it would suggest that having a common threshold applied to all the different pathologies may dilute the sensitivity/specificity of the test. The effect of this will need to be evaluated in a larger cohort of patients.

The use of conventional surface ECG and ECGi electrophysiological parameters has been previously explored in a group of patients that form part of this study cohort, where SCD survivors possessed the greatest amount of dispersion of repolarisation and regional conduction abnormalities following exertion.[8] It would stand to reason that the lowest V-CoS

scores found in SCD survivors are the result of these electrophysiological perturbations detected by conventional means. As to what degree repolarisation abnormalities may also be reflected by this score or the additive effect of other ECGi electrophysiological parameters remains to be investigated.

In comparison to conventional risk stratification techniques for BrS and HCM, V-CoS testing would appear to have greater accuracy to identify individuals at high risk of SCD. In those with idiopathic VF/VT, there is an absence of a formal *apriori* risk stratification system. In one of our patients with iVF, an ICD had been implanted for primary prevention following a multidisciplinary discussion at our institute. This was made on the basis of ongoing intermittent palpitations, a family history of SCD and having a similar ECG of T wave inversion in the inferior leads to her deceased brother. All other investigations were normal (including Holter, exercise ECG and MRI). Three years later, she received an appropriate shock for VF from her device with no other apparent cardiac abnormality on subsequent clinical work up. Her V-CoS score was 86.5%, below the threshold of 96.4% as defined on ROC analysis.

Study Considerations

Given the small numbers within each subgroup, a prospective study involving a much larger group of patients is required to validate these findings before this may be translated into clinical management.

Factors such as gender and age may affect sensitivity/specificity of the test although numbers in this study are too small to allow meaningful analysis. Although no significant differences

were observed between comparative study groups, the effects of such factors on the sensitivity and specificity of V-CoS testing will be need to be explored in future studies.

We assume ECGi provides a reasonable reflection of epicardial activation patterns based on previous validation work of the system, but also acknowledge the limitations in its reconstructive accuracy.[9] As we are quantifying magnitude of change within an individual using the same heart-torso geometry data and have algorithms in place to resolve annotation issues that can arise as described previosuly,[9] we believe these factors are less of an issue.

We have not tested whether low V-CoS scores observed in the SCD group might be the result of a previous episode of VF or defibrillation. However, this would be unlikely because some patients within the aborted SCD group have relative high V-CoS scores.

V-CoS is described as intended to address only timings of activation. We do not know to what extent it is associated with repolarisation abnormalities. Direct measures of repolarisation may further discriminate those at high risk.

There is beat to beat variability in measurements which could impair the diagnostic ability of V-CoS. However, in a previous study this variability appeared to be small[9].

Finally autonomic tone can be variable and the reproducibility of this test on a different day is unknown. We acknowledge that the aforementioned factors may theoretically compound variability in measurements of V-CoS scores and requires further study. Whilst this could be explored in future, it would require double radiation because each day's vest positioning would need its own CT thorax. In summary, these results and the non-invasive nature of the test have important implications for risk stratification but require a large prospective study to validate these findings

Conclusion

This study demonstrates the potential discriminative ability of the V-CoS test and its application in different types of ICC patients as a tool to measure the electrophysiological substrate that predisposes to ventricular fibrillation. The V-CoS test described provides a novel approach to automatically quantify alterations in whole heart activation patterns which may help better identify those with an inheritable cardiac condition and at increased risk of ventricular arrhythmias.

References

1. Han J, Moe GK. Nonuniform Recovery of Excitability in Ventricular Muscle. *Circ Res*. 1964;14:44-60. doi:10.1161/01.RES.14.1.44
2. Antzelevitch C. Role of spatial dispersion of repolarization in inherited and acquired sudden cardiac death syndromes. *Am J Physiol Heart Circ Physiol*. 2007;293(4):2024-2038. doi:10.1038/jid.2014.371
3. Nishii N, Nagase S, Morita H, Kusano KF, Namba T, Miura D et al. Abnormal restitution property of action potential duration and conduction delay in Brugada syndrome: both repolarization and depolarization abnormalities. *Europace*. 2010;12(4):544-552. doi:10.1093/europace/eup432
4. Saumarez RC, Heald S, Gill J, Slade AKB, de Belder M, Walczak F et al. Primary Ventricular Fibrillation Is Associated With Increased Paced Right Ventricular Electrogram Fractionation. *Circulation*. 1995;92(9):2565-2571. doi:10.1161/01.CIR.92.9.2565
5. Cao JM, Qu Z, Kim YH, Wu TJ, Garfinkel A, Weiss JN et al. Spatiotemporal heterogeneity in the induction of ventricular fibrillation by rapid pacing: Importance of cardiac restitution properties. *Circ Res*. 1999;84(11):1318-1331. doi:10.1161/01.RES.84.11.1318
6. Ng GA, Brack KE, Patel VH, Coote JH. Autonomic modulation of electrical restitution, alternans and ventricular fibrillation initiation in the isolated heart. *Cardiovasc Res*. 2007;73(4):750-760. doi:10.1016/j.cardiores.2006.12.001
7. Priori S, Blomström-Lundqvist C, Mazzanti A, Blom N, Borgreffe M, Camm JA et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;8:746-837. doi:10.1093/europace/eul108

8. Leong KMW, Ng FS, Roney C, et al. Repolarization abnormalities unmasked with exercise in sudden cardiac death survivors with structurally normal hearts. *J Cardiovasc Electrophysiol*. 2018;29:115-126. doi:10.1111/jce.13375
9. Shun-Shin MJ, Leong KMW, Ng FS, Cantwell C, Shun-Shin MJ, Linton N et al. Ventricular conduction stability test: a method to identify and quantify changes in whole heart activation patterns during physiological stress. EP Eur. 2019. doi:10.1093/europace/euz015
10. Youden WJ. Index for rating diagnostic tests. *Cancer*. 1950;3:32-35. doi:10.1002/1097-0142(1950)3:1<32::AID-CNCR2820030106>3.0.CO;2-3
11. O'Mahony C, Jichi F, Pavlou M, Lorenzo M, Anastasakis A, Rapezzi C et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD). *Eur Heart J*. 2014;35(30):2010-2020. doi:10.1093/eurheartj/eht439
12. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35:2733-2779. doi:10.1093/eurheartj/ehu284
13. Varnava AM, Elliott PM, Baboonian C, Davison F, Davies MJ, McKenna WJ. Hypertrophic cardiomyopathy: Histopathological features of sudden death in cardiac troponin T disease. *Circulation*. 2001;104:1380-1384. doi:10.1161/hc3701.095952
14. Lambiase PD, Ahmed AK, Ciaccio EJ, Brugada E, Lizotte E, Chaubey S et al. High-density substrate mapping in Brugada syndrome: combined role of conduction and repolarization heterogeneities in arrhythmogenesis. *Circulation*. 2009;120(2):106-117. doi:10.1161/CIRCULATIONAHA.108.771401

15. Zhang J, Sacher F, Hoffmayer K, O'Hara T, Strom M, Cuculich P et al. Cardiac electrophysiological substrate underlying the ECG phenotype and electrogram abnormalities in brugada syndrome patients. *Circulation*. 2015;131:1950-1959. doi:10.1161/CIRCULATIONAHA.114.013698
16. Papadakis M, Petzer E, Sharma S. Unmasking of the Brugada phenotype during exercise testing and its association with ventricular arrhythmia on the recovery phase. *Heart*. 2009;95:2022. doi:10.1136/hrt.2009.174052
17. Elliott PM, Sharma S, Varnava A, Poloniecki J, Rowland E, McKenna WJ. Survival after cardiac arrest or sustained ventricular tachycardia in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 1999;33(6):1596-1601. doi:10.1016/S0735-1097(99)00056-X
18. Makimoto H, Nakagawa E, Takaki H, Yamada Y, Okamura H, Noda T et al. Augmented ST-segment elevation during recovery from exercise predicts cardiac events in patients with brugada syndrome. *J Am Coll Cardiol*. 2010;56(19):1576-1584. doi:10.1016/j.jacc.2010.06.033
19. Link MS, Bockstall K, Weinstock J, Alsheikh-Ali A, Semsarian C, Estes NAM et al. Ventricular Tachyarrhythmias in Patients With Hypertrophic Cardiomyopathy and Defibrillators: Triggers, Treatment, and Implications. *J Cardiovasc Electrophysiol*. 2017;28(5):531-537. doi:10.1111/jce.13194
20. Peeters HAP, Sippensgroenewegen A, Wever EFD, Potse M, Daniels MCG, Grimbergen CA et al. Electrocardiographic identification of abnormal ventricular depolarization and repolarization in patients with idiopathic ventricular fibrillation. *J Am Coll Cardiol*. 1998;31:1406-1413. doi:10.1016/S0735-1097(98)00120-X

Figure Legends

Figure 1 – Body surface potential data are obtained from the EcVue 252 electrode vest and are combined with heart torso geometry obtained from patient's CT thorax (i-iv). ECGi reconstructs >1200 unipolar electrograms over the cardiac surface and 3D activation maps of beats obtained at peak exertion and the reference baseline following exercise treadmill testing (v). Electrogram data are inputted into the V-CoS programme that produces a score (0-100%) to indicate the development of spatial heterogeneities in conduction (vi).

Figure 2 - Median and interquartile V-CoS scores following exertion in SCD and non-SCD groups

Figure 3 – Trend of V-CoS scores post exertion in SCD and non-SCD patients in the different subgroups of patients i) idiopathic ventricular fibrillation/tachycardia (iVF/VT) ii) Brugada Syndrome (BrS) iii) Hypertrophic Cardiomyopathy (HCM). Median and interquartile ranges values are shown. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Figure 4 – Comparison of minimum V-CoS scores obtained post exertion between SCD and non-SCD patients in the different subgroups. Median and interquartile ranges values are shown. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Figure 5 – Receiver operating characteristics (ROC) curves showing the predictive performance of the V-CoS test when applied to a) all patients b) iVF/VT and structurally normal hearts c) Brugada Syndrome and d) Hypertrophic Cardiomyopathy.

Figure 6 – Comparison of VCoS with conventional risk stratification for BrS

Figure 7 – Comparison of VCoS with conventional risk stratification for HCM

i) 252 electrode vest
ii) Body surface potentials
iii) Transverse CT images
iv) Heart Torso geometry
ECGi Software
v) ECGi Reconstruction of activation map and electrograms from beats at:
vi) V-CoS programme
RV
LAD
RVOT
Anterior posterior view
Reference phase (e.g resting baseline)
Test phase (e.g post exertion)
Reference phase
Test phase
Relative Time Difference
+16
+8
+0
-3
-7
-7
40
Activation Time (ms)
75
100ms
1mV
-20
Relative Time Delay (ms)
+20
Legend
RV – Right Ventricle
LV – Left Ventricle
LAD – Left Anterior Descending Artery
Electrogram data from both beats are inputed into V-CoS programme to derive V-CoS scores ≤100%
Where 100% denotes unchanged activation patterns between rest and exercise, and lower VCoS scores denote greater degrees of spatial heterogeneity developing.

Figure 1

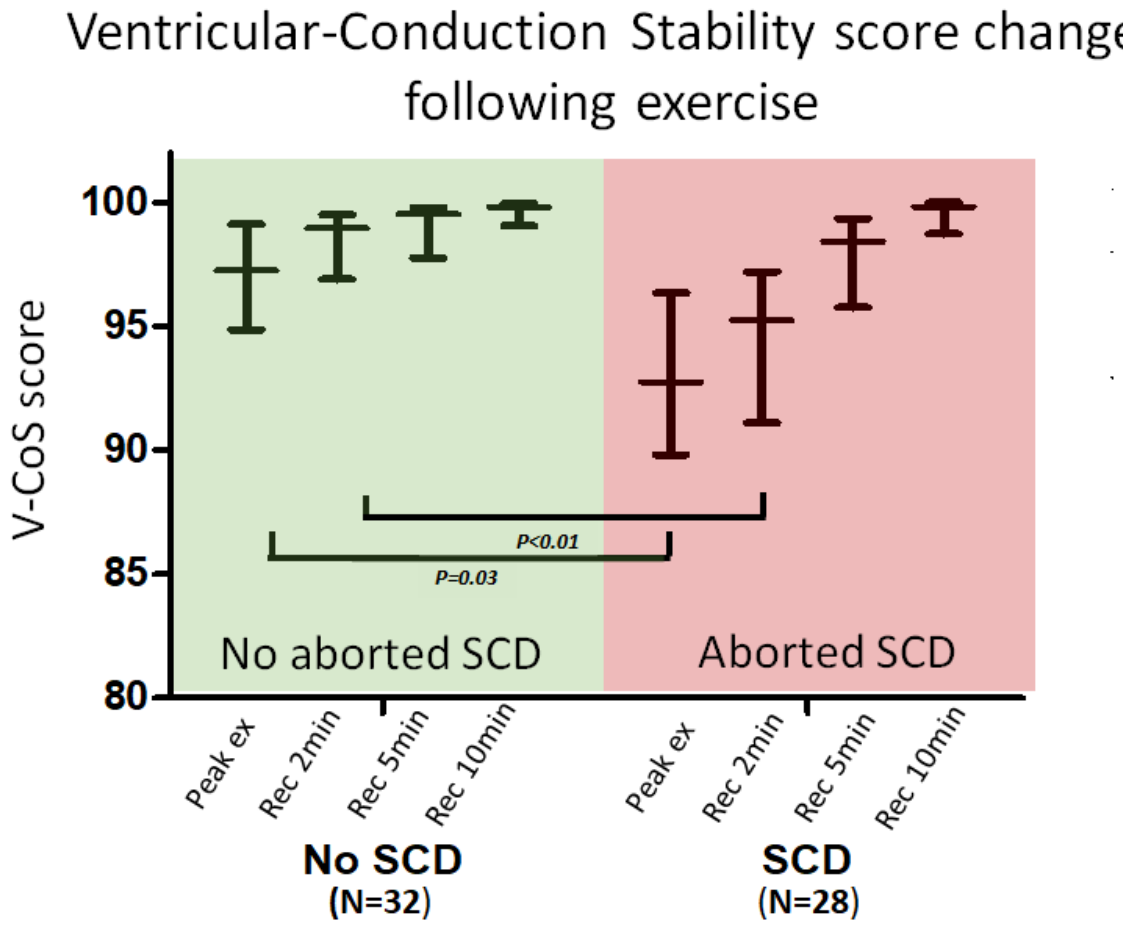
Ventricular-Conduction Stability score change following exercise
V-CoS score
100
95
90
85
80
P<0.01
P=0.03
No aborted SCD
Aborted SCD
Peak ex
Rec 2min
Rec 5min
Rec 10min
Peak ex
Rec 2min
Rec 5min
Rec 10min
No SCD
(N=32)
SCD
(N=28)

Figure 2

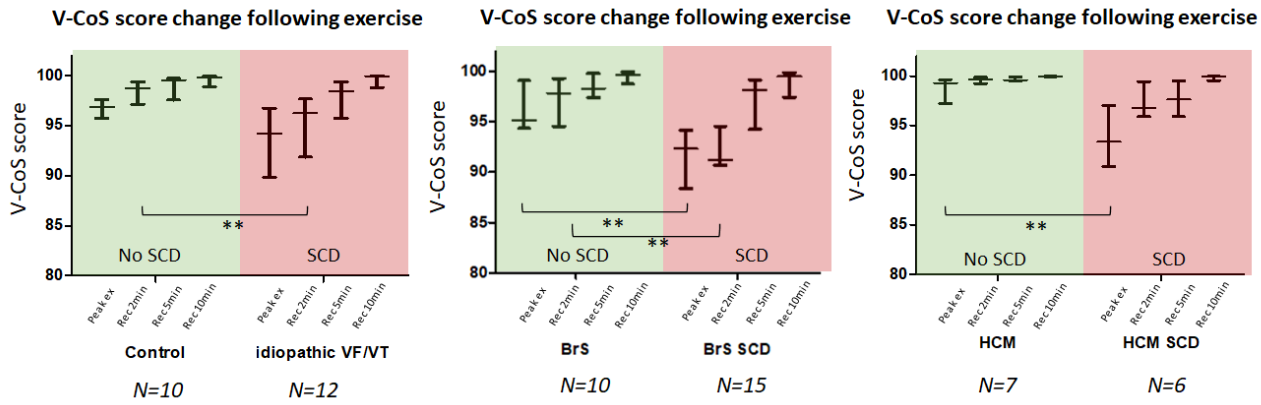
V-CoS score change following exercise
V-CoS score
100
95
90
85
80
No SCD
SCD
**
Peak ex
Rec 2min
Rec 5min
Rec 10min
Control
idiopathic VF/VT
N=10
N=12
V-CoS score change following exercise
BrS
BrS SCD
N=10
N=15
V-CoS score change following exercise
HCM
HCM SCD
N=7
N=6

Figure 3

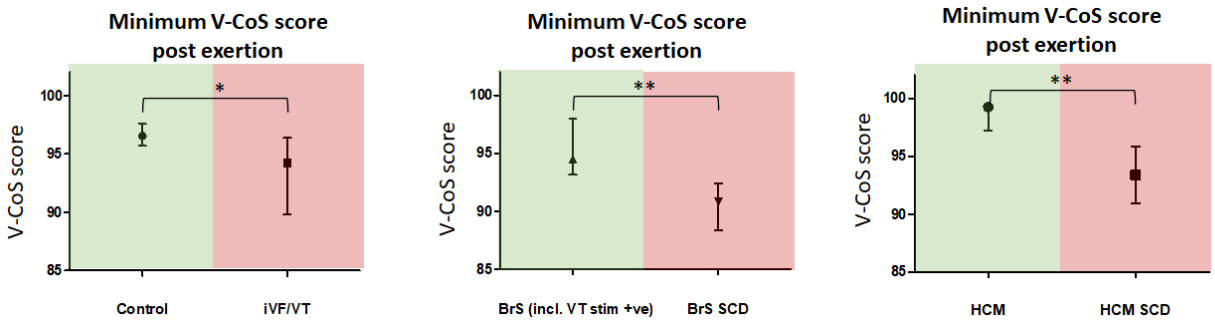
Minimum V-CoS score post exertion
V-CoS score
100
95
90
85
*
Control
iVF/VT
Minimum V-CoS score post exertion
V-CoS score
100
95
90
85
**
BrS (incl. VT stim +ve)
BrS SCD
Minimum V-CoS score post exertion
V-CoS score
100
95
90
85
**
HCM
HCM SCD

Figure 4

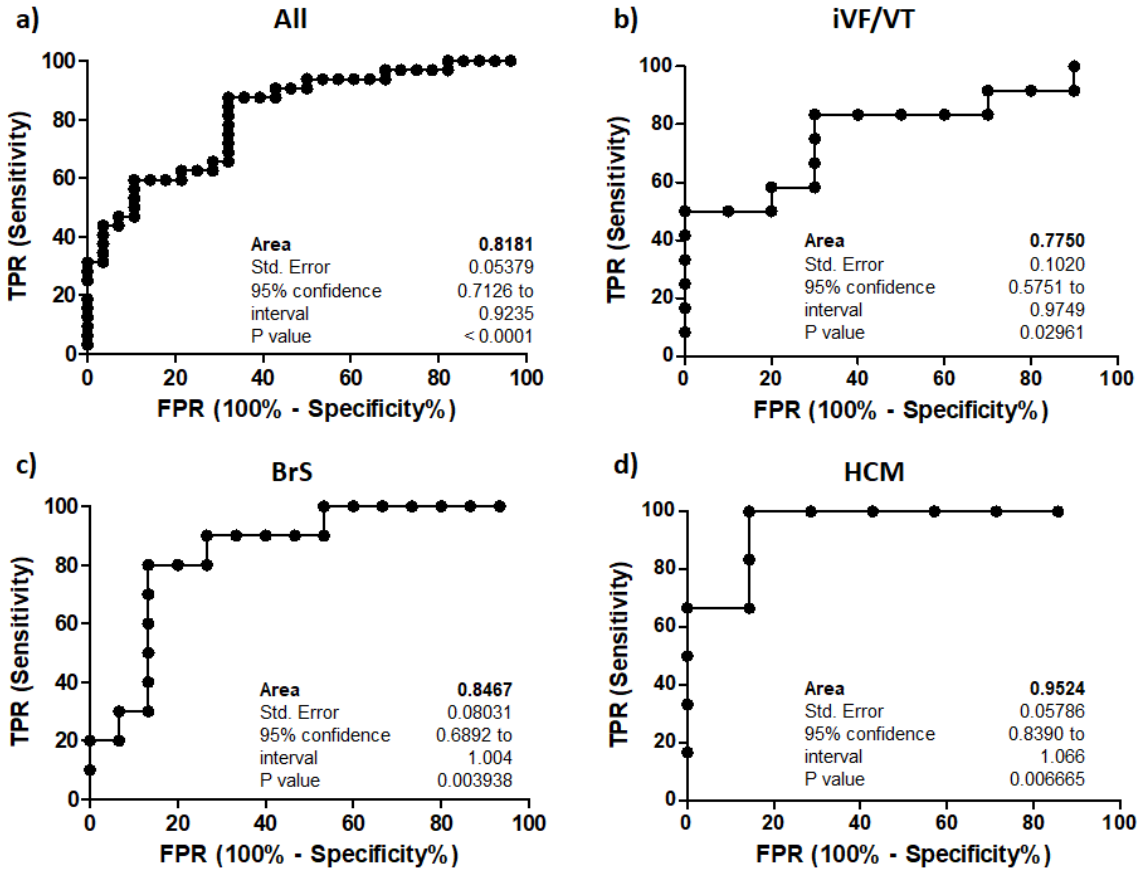
a)
All
TPR (Sensitivity)
FPR (100% - Specificity%)
Area 0.8181
Std. Error 0.05379
95% confidence interval 0.7126 to 0.9235
P value < 0.0001
b)
iVF/VT
TPR (Sensitivity)
FPR (100% - Specificity%)
Area 0.7750
Std. Error 0.1020
95% confidence interval 0.5751 to 0.9749
P value 0.02961
c)
BrS
TPR (Sensitivity)
FPR (100% - Specificity%)
Area 0.8467
Std. Error 0.08031
95% confidence interval 0.6892 to 1.004
P value 0.003938
d)
HCM
TPR (Sensitivity)
FPR (100% - Specificity%)
Area 0.9524
Std. Error 0.05786
95% confidence interval 0.8390 to 1.066
P value 0.006665

Figure 5

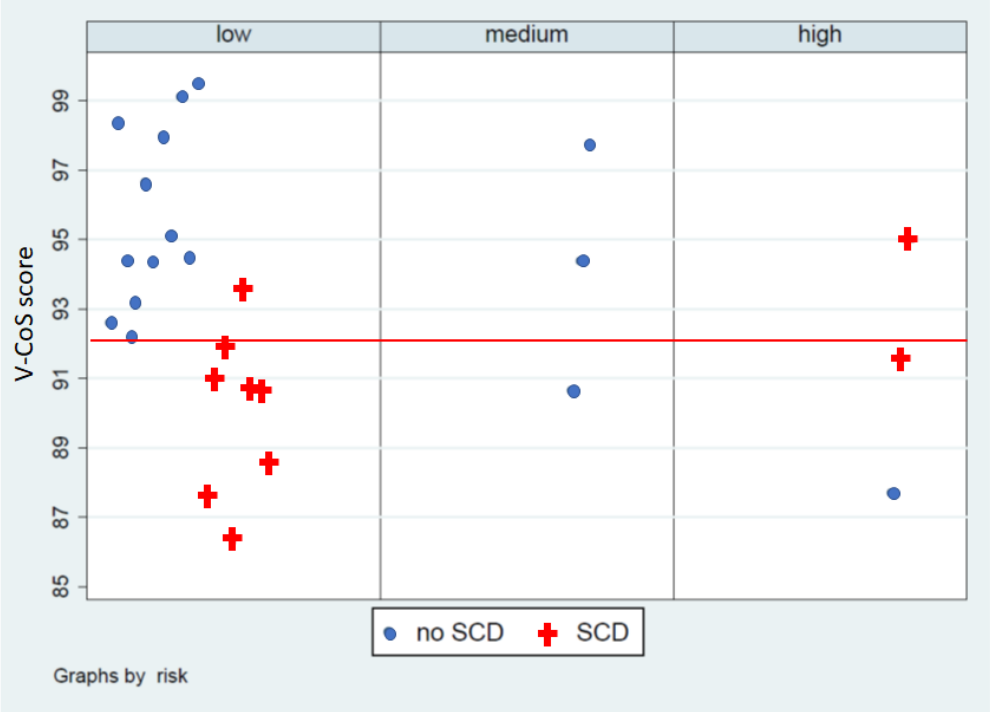
low
medium
high
V-CoS score
99
97
95
93
91
89
87
85
no SCD
SCD
Graphs by risk

Figure 6

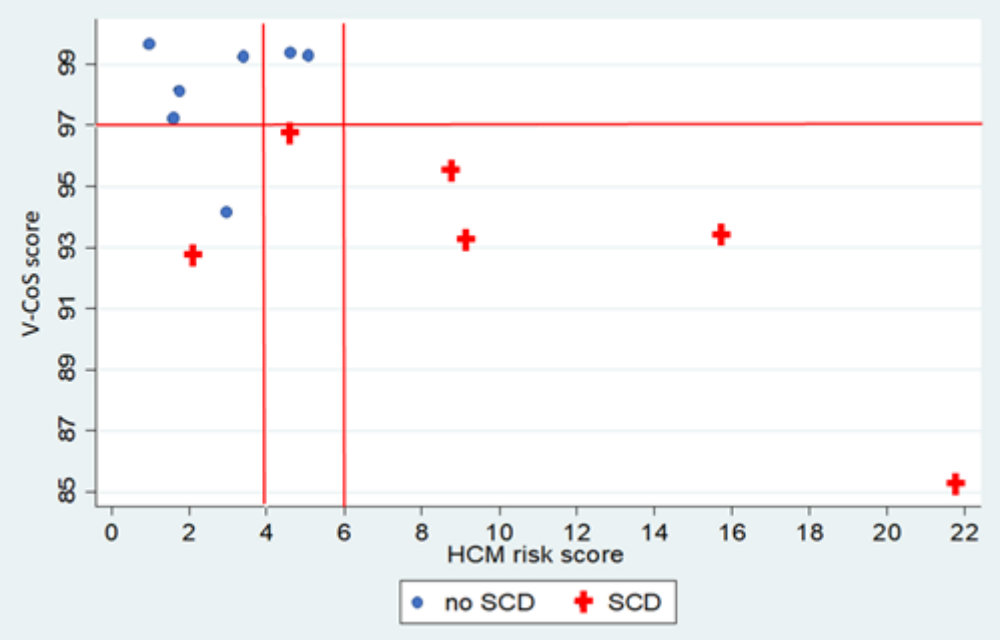
V-CoS score
85
87
89
91
93
95
97
99
0
2
4
6
8
10
12
14
16
18
20
22
HCM risk score
no SCD
SCD

Figure 7

	NSCD (n=32)	SCD (n=28)	P value*
V-CoS scores			
Peak Exertion	97.3% (94.9-99.1%)	92.8% (89.8-96.3%)	*P<0.05*
Recovery 2 minutes	98.9% (96.9-99.5%)	95.2% (91.1-97.2%)	*P<0.01*
Recovery 5 minutes	99.5% (97.8-99.8%)	98.4% (95.8-99.3%)	*P=ns*
Recovery 10 minutes	99.8% (99.1-100%)	99.8% (98.7-100%)	*P=ns*
Heart rate			
Peak Exertion	137 (120-153)	138 (129-155)	*P=ns*
Recovery 2 minutes	94 (88-108)	101 (90-112)	*P=ns*
Recovery 5 minutes	90 (80-99)	91 (84-96)	*P=ns*
Recovery 10 minutes	88 (78-95)	87 (83-98)	*P=ns*

Table 1 - Summary of median (interquartile range) V-CoS scores and heart rate at each stage of recovery post exertion. *Dunn's multiple comparison test was applied. *ns* - not significant.