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

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BRC.

Abstract

Introduction:
Rate adaptation of the action potential ensures spatial heterogeneities in conduction across the
myocardium are minimised at different heart rates which provides a protective mechanism
against the development of ventricular fibrillation (VF) and sudden cardiac death (SCD). We
preciously described the Ventricular Conduction Stability (V-CoS) test which rapidly
quantifies changes in ventricular activation during cardiac cycle length changes. We tested
the hypothesis that patients with a history of aborted SCD due to an underlying channelopathy or cardiomyopathy (SCD) 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 (BrS), 13
Hypertrophic Cardiomyopathy (HCM), 12 idiopathic VF (iVF) and 10 healthy controls. Data
was processed by the V-CoS programme to calculate the relative change in EGM local
activation times (LAT) for every point over the ventricular surface between a reference
baseline state and post exertional state for each patient. A V-CoS score was calculated to
indicate the percentage of ventricle that showed no significant change in LAT (<10ms), 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%(94.9-99.1%) 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 significant
lower score than those without for each of the different underlying aetiologies.

Conclusion:

We present 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.
Introduction

Arrhythmogenic mutations in inherited cardiac conditions (ICCs) 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 arrhythmogenesis 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 a universal discriminator for the different ICCs. 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 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. Patients with structurally normal hearts with no history of syncope or family history of sudden death/ICC undergoing electrophysiological studies for ventricular ectopy or supra-ventricular tachycardia 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-cardiographical 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.

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). 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. Briefly, the programme allows the rapid 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.

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.
**Data analysis**

Electrogram data was analysed at 10 minutes, 5 minutes, 2 minutes and within a minute of cessation of exercise on the treadmill (defined as peak exertion) for each individual. 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. The Youden’s index, defined as $\text{sensitivity}+\text{specificity}-1.00$, was calculated for all points on the ROC curve. 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, 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. For calculation of the score in SCD survivors, a prior history of syncope was considered present if occurred before their presenting SCD event. High risk individuals were deemed as those having a 5 year risk of >6%; Intermediate risk – 4 to 6%; Low risk - <4%.

Statistical analysis

Determination of parametric and non-parametric variables was performed using the D'Agostino-Pearson normality test with values presented as mean ± standard deviation (SD) or median ± inter-quartile range (IQR) respectively. For non-parametric 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 Man-Whitney test was employed for comparison between two groups with the Dunn’s correction where multiple comparisons were required. For parametric variables, the t-test or ANOVA test was employed for comparison of two or three groups respectively. 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 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 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 5). There were no significant differences in heart rate between groups at each stage of recovery (Table 5).

**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).
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). 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).

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

Area under the ROC (AUROC) curve was 0.82 when applied to all patients in this study. The AUROC 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’s index, a cut-off 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 score at 92.3% derived from Youden’s index, provided a sensitivity and specificity of 80.0%/86.7%. In HCM, a threshold at 97.0% provided a sensitivity and specificity at 100%/85.7%. A Youden’s index derived threshold of 96.4% in iVF/VT provided a sensitivity and specificity of 83.3%/70.0%.

In the BrS cohort, conventional risk stratification based on the presence of a spontaneous Type I BrS pattern and syncope would have correctly 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% correctly identified 80% of the SCD cohort as high risk (Figure 6). The AUROC curve for the V-CoS test in the HCM subgroup (0.95) was 0.14 higher than AUROC curve 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 an increase in non-uniform recovery of excitation 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.

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.\(^{16,17,19,21}\)

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.
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. 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.

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. Another consideration to explore is if the low V-CoS scores observed in the SCD group could be affected by previous episode of VF or defibrillation. Such a supposition would be unlikely given that some patients within the aborted SCD group have relative high V-CoS scores. Whilst V-CoS detects alterations in conduction, we assume it also provides a surrogate for repolarisation abnormalities as well. Direct measures of repolarisation may further discriminate those at high risk and may account for those within the SCD group with relatively high V-CoS scores. Given that beat to beat variability was previously shown to be low⁹, we also assumed that such variation remained similar between individuals despite different underlying aetiologies. Finally, as autonomic tone can be
variable, the reproducibility of this test on a different day needs to be explored further with consideration given to the additional radiation from a repeat CT thorax.

**Conclusion**

This study demonstrates the 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. 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.
References


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 programmed into the V-CoS programme that produces a score (0-100%) to indicate the development of spatial heterogeneities in conduction.

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 Torsion geometry
- v) Reconstruction of activation map and electrograms from beats at:
  - a) Peak exertion
  - b) Full recovery
- v) V-CoS programme

Electrogram data from both beats are inputted into V-CoS programme to derive V-CoS scores between 0-100%
100% = identical activation between rest and exercise
0% = rest and exercise activation patterns completely heterogeneous
Ventricular-Conduction Stability score change following exercise

Figure 2
Figure 3
Figure 4
Figure 5
Figure 6
Figure 7
Table 1 – Group characteristics of patients with BrS with and without previous SCD event

<table>
<thead>
<tr>
<th></th>
<th>BrS n=15</th>
<th>BrS-SCD n=10</th>
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<tr>
<td>Mean age</td>
<td>46±12</td>
<td>43±10</td>
</tr>
<tr>
<td>Gender M:F</td>
<td>10:5</td>
<td>9:1</td>
</tr>
<tr>
<td>Presentation</td>
<td>12 family screen; 3 Type I/II with fever</td>
<td>10 OOH VF; 2 OOH CPR</td>
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<tr>
<td>Spon. Type I</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Prior Syncope</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>PES +ve</td>
<td>4</td>
<td>n/a</td>
</tr>
<tr>
<td>Normal Echo/MRI</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td><strong>HCM</strong></td>
<td><strong>HCM-SCD</strong></td>
</tr>
<tr>
<td>--------------------------</td>
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</tr>
<tr>
<td><strong>Mean age</strong></td>
<td>49±9</td>
<td>44±14</td>
</tr>
<tr>
<td><strong>Gender M:F</strong></td>
<td>7:0</td>
<td>5:1</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>3 family screening; 3 incidental finding; 2 symptoms</td>
<td>5 VF/VT; 1 OOH CPR</td>
</tr>
<tr>
<td><strong>HCM risk score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4%</td>
<td>5 (71%)</td>
<td>1 (16.5%)</td>
</tr>
<tr>
<td>4-6%</td>
<td>2 (29%)</td>
<td>1 (16.5%)</td>
</tr>
<tr>
<td>&gt;6%</td>
<td>0</td>
<td>4 (67%)</td>
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Table 2 – Group characteristics of patients with HCM with and without previous aborted SCD equivalent event
Table 3 – Group characteristics of patients with sustained episode of ventricular fibrillation/tachycardia requiring resuscitation.

<table>
<thead>
<tr>
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<th>Idiopathic VF n=12</th>
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<td>Mean age</td>
<td>37±8</td>
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<tr>
<td>Gender M:F</td>
<td>10:2</td>
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<tr>
<td>Presentation</td>
<td>11 OOH VF/VT requiring cardioversion</td>
</tr>
<tr>
<td>Normal Ajmaline challenge</td>
<td>12</td>
</tr>
<tr>
<td>Normal Adrenaline/ETT challenge</td>
<td>12</td>
</tr>
<tr>
<td>Normal Angio</td>
<td>12</td>
</tr>
<tr>
<td>Normal Echo/MRI</td>
<td>12</td>
</tr>
<tr>
<td>Characteristics</td>
<td>Controls n=10</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Mean age</td>
<td>37±12</td>
</tr>
<tr>
<td>Gender M:F</td>
<td>4:6</td>
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<tr>
<td>Diagnosis</td>
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<tr>
<td>Ventricular ectopy</td>
<td>5</td>
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<td>Atrial ectopy</td>
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<td>AVNRT</td>
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<tr>
<td>Normal ECG/ETT</td>
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<tr>
<td>No FHx ICC/SCD</td>
<td>10</td>
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<tr>
<td>Normal Echo/MRI</td>
<td>14</td>
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Table 4 – Group characteristics of control patients
<table>
<thead>
<tr>
<th></th>
<th>NSCD (n=32)</th>
<th>SCD (n=28)</th>
<th>P value*</th>
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<tbody>
<tr>
<td><strong>V-CoS scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak Exertion</td>
<td>97.3% (94.9-99.1%)</td>
<td>92.8% (89.8-96.3%)</td>
<td><em>P&lt;0.05</em></td>
</tr>
<tr>
<td>Recovery 2 minutes</td>
<td>98.9% (96.9-99.5%)</td>
<td>95.2% (91.1-97.2%)</td>
<td><em>P&lt;0.01</em></td>
</tr>
<tr>
<td>Recovery 5 minutes</td>
<td>99.5% (97.8-99.8%)</td>
<td>98.4% (95.8-99.3%)</td>
<td>ns</td>
</tr>
<tr>
<td>Recovery 10 minutes</td>
<td>99.8% (99.1-100%)</td>
<td>99.8% (98.7-100%)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak Exertion</td>
<td>137 (120-153)</td>
<td>138 (129-155)</td>
<td>ns</td>
</tr>
<tr>
<td>Recovery 2 minutes</td>
<td>94 (88-108)</td>
<td>101 (90-112)</td>
<td>ns</td>
</tr>
<tr>
<td>Recovery 5 minutes</td>
<td>90 (80-99)</td>
<td>91 (84-96)</td>
<td>ns</td>
</tr>
<tr>
<td>Recovery 10 minutes</td>
<td>88 (78-95)</td>
<td>87 (83-98)</td>
<td>ns</td>
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</table>

Table 5 - 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.