Study Protocol for,

The prevalence and significance of low QRS voltages in young healthy individuals and athletes

Version 4
Date: 22/06/2023

MAIN SPONSOR: **Imperial College London**
FUNDERS: **Royal Brompton Hospital Charity/Cardiac Risk in the Young**
STUDY COORDINATION CENTRE: **Royal Brompton Hospital**

IRAS Project ID: *283055*
REC reference: 23/PR/0361
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Protocol for non-CTIMP

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IRAS Project ID: *283055*
REC reference: 23/PR/0361

Protocol authorised by:

Name & Role	Date	Signature
Dr Sabiha Gati	31/10/2022	

Study Management Group

Chief Investigator: Dr Sabiha Gati

Co-investigators: Professor Sanjay Sharma, Professor Dudley Pennell, Dr Nirmitha Jayaratne

Statistician: Winston Banya

Study Management: Dr Nirmitha Jayaratne

Study Coordination Centre - Royal Brompton Hospital

For general queries, supply of study documentation, and collection of data, please contact:

Study Coordinator: Dr Sabiha Gati
Address: Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK
Registration: GMC 6106246
Tel: *07966660767* E-mail: S.gati@rbht.nhs.uk
Fax: N/A Web address: N/A

Clinical Queries

Clinical queries should be directed to Dr Nirmitha Jayaratne who will direct the query to the appropriate person

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Research Governance and Integrity Team
Imperial College London and Imperial College Healthcare NHS Trust
Room 215, Level 2, Medical School Building
Norfolk Place
London, W2 1PG
Tel: **0207 594 1862**
Imperial College - Research Governance and Integrity Team (RGIT) Website

Funder:

Cardiac Risk in the Young Charity

This protocol describes the "**The prevalence and significance of low QRS voltages in young healthy individuals and athletes"** study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

LQRSV	Low QRS Voltage
SCD	Sudden Cardiac Death
CMR	Cardiac Magnetic Resonance
ECG	Electrocardiogram
TFTs	Thyroid function tests
PVCs	Premature Ventricular complexes
DCM	Dilated Cardiomyopathy
ARVC	Arrhythmogenic right ventricular cardiomyopathy
LGE	Late Gadolinium Enhancement
CPET	Cardiopulmonary exercise testing
ICD	Implantable cardioverter defibrillator
VO2	Baseline oxygen consumption
AT	Anaerobic threshold
V˙E/V˙CO2	Ventilatory efficiency for carbon dioxide
RER	Respiratory exchange ratio

KEYWORDS

Low QRS Voltage
Low QRS amplitude
Sudden Cardiac Death
Cardiac magnetic resonance
Myocardial fibrosis
Premature Ventricular complexes

Dilated Cardiomyopathy
Arrhythmogenic right ventricular cardiomyopathy
Late Gadolinium Enhancement
Implantable cardioverter defibrillator
Cardiopulmonary exercise testing
Athletes
Genetic inheritance
Non sustained ventricular tachycardia

STUDY SUMMARY

TITLE **The prevalence and significance of low QRS voltages in young healthy individuals and athletes**

DESIGN Cross sectional Observational study

AIMS The study aims to investigate the prevalence and significance of low QRS voltages in young healthy individuals and athletes aged 17-35 years old.

OUTCOME MEASURES **1.** Prevalence of low QRS voltages in athletes and young non-athletic population on ECG analysis.

2. Prevalence of myocardial fibrosis in the young athletic and non-athletic population with low QRS.

Exploratory secondary outcomes:

- The proportion of individuals with low QRS complexes and myocardial fibrosis with rare protein altering variant in a cardiomyopathy gene.
- Exercise related ventricular premature beats or a ventricular premature beat burden of > 500 beats on a Holter monitor.

POPULATION 240 total study population: 60 athletes with low QRS voltage and 60 age and sex matched control group of athletes with normal QRS voltage, 60 non-athletes with low QRS voltage and 60 sex and age matched controls with normal QRS voltage

ELIGIBILITY Inclusion criteria for athletes and non-athletes with low QRS complexes: Asymptomatic and body mass index <30.

Exclusion Criteria for Controls and Athletes: Individuals with cardiac symptoms; past medical history of cardiac disease; family history of SCD <40 years old or cardiomyopathy; previous myocarditis; lung disease; individuals with pacemakers, defibrillators; pregnant women; advanced kidney and/or liver disease; no known thyroid disease, T-wave inversion or other training unrelated ECG changes, significant valvular heart disease or intra-cardiac shunt on echocardiography.

DURATION 2022- 2027

1. INTRODUCTION

1.1. BACKGROUND

Low QRS Voltages in the Limb Leads in the general population: There is limited evidence in the literature that low QRS voltages (defined as QRS amplitude of <0.5mV in the limb leads) may be associated with left ventricular myocardial fibrosis and a predisposition to serious ventricular arrhythmias and SCD.[1,2,5] Low QRS voltages on the 12-lead ECG are thought to reflect conditions that impair the transmission of electrical signals in the heart. The prevalence of low QRS complexes in the general population is between 0.3-2%.[5–8] However, this includes individuals with chronic obstructive pulmonary disease, undiagnosed hypothyroidism, obesity, large pleural and pericardial effusion, severe left ventricular systolic dysfunction and infiltrative cardiomyopathies, which are also associated with low voltages.[6,7,17–20,9–16] **The prevalence of low QRS voltages and their significance in young healthy individuals (17-35 years old) is not fully understood.**

Low QRS Voltages in the Limb Leads in Athletes: Sudden cardiac death (SCD) is one of the leading causes of death in athletes .[21–23] The majority of deaths are attributable to hereditary, structural or electrical pathologies which can be identified by abnormalities on the resting 12-lead ECG. Distinguishing physiological changes due to regular physical training resulting from increased vagal tone and increased chamber size and wall thickness [24] from those of potentially life threatening cardiac conditions can be challenging. The 2010 European Society of Cardiology recommendations for ECG interpretation in athletes[25] and the more recent international recommendations[26] provide a clear guide to aid ECG interpretation in athletes and are supported by a growing evidence base[24].

Low QRS voltages (<0.5mV in the limb leads and <1.0 mV in the precordial leads) do not feature in the current international recommendations[27] due to a lack of robust evidence. In a recent study in Italian competitive athletes demonstrated that the prevalence of low QRS voltages was 1.1%.[5] Five athletes with low QRS voltages and exercise induced arrhythmias underwent CMR showing biventricular arrhythmogenic cardiomyopathy or idiopathic myocardial scar in two individual. n another study involving Italian Olympian athletes demonstrated that the prevalence of low QRS voltages of 4%.[28] All athletes were investigated with ECG, echocardiography, maximal exercise test and 24-hour Holter recoding. The researchers did not identify any correlation between low QRS voltages and left ventricular morphology on echocardiography although premature ventricular beats were more frequent in athletes with low QRS voltages compared with athletes with normal QRS voltages (39% vs 7%). Furthermore, no cardiac events were recorded over a follow-up period of 5±2 years. **The main limitation of this study is that athletes with low QRS voltages did not have CMR for the assessment of myocardial fibrosis.** In a study of 35 competitive athletes with isolated non-ischaemic LV scar by CMR and ventricular arrhythmias, Zorzi et al reported that 20% of this cohort exhibited low QRS voltages.[4] **A larger study in athletes and healthy individuals with low QRS voltages versus a control population using CMR is required.**

Cardiovascular Magnetic Resonance in Athletes: There has been a substantial rise in the use of CMR for assessing athletes with ECG repolarisation changes. CMR has high reproducibility and provides detailed tissue characterisation. CMR with gadolinium contrast provides the unique ability to detect myocardial inflammation and fibrosis. T1 mapping enables the detection of interstitial fibrosis and T2 mapping detects myocardial oedema. Assessment of extracellular volume (ECV) provides quantitative assessment of cellular vs

extracellular composition. Such techniques can play a pivotal role in understanding tissue changes contributing to low QRS voltages.

1.2. RATIONALE FOR CURRENT STUDY

The limitations of the above studies described are that not all athletes with low QRS voltages undertook a CMR evaluation to determine sensitivity, specificity, and positive predictive value of disease prediction. Therefore there is a need for a larger study in athletes and healthy individuals with low QRS voltages versus a control population using CMR to further evaluate the findings on these studies.

We postulate that left ventricular lateral/inferior wall subepicardial wall myocardial fibrosis in young individuals and athletes manifests as small QRS voltages on the ECG. In turn, myocardial fibrosis in athletes and young non-athletic individuals may reflect a pathogenic or likely pathogenic mutation in genes associated with cardiomyopathies. Such an approach to evaluating low QRS voltages in athletes should ultimately help determine the precise significance of small QRS complexes in young apparently healthy non-athletic individuals and athletes. The outcomes will facilitate the development of new recommendations on ECG interpretation in young individuals and athletes and identify young people at risk of SCD.

We hypothesise that in athletes and non-athletic subjects aged 17-35 years old with low QRS voltages: 1. The prevalence of myocardial fibrosis is greater. 2. The prevalence of known/likely pathogenic mutations in genes associated with DCM/AVC is greater.

2. STUDY OBJECTIVES

Primary objective is to investigate the prevalence and significance of low QRS voltages in young healthy individuals and athletes aged 17-35 years old.

This study will also aim to inform updated current international recommendations on ECG interpretation in athletes. The results of this study will have an impact on athletes worldwide, even if an ICD was not implanted there are several measures that would mitigate the risk of sudden death such as advise to abstain from vigorous exercise, regular surveillance for risk stratification, screening of first-degree relatives to identify others who may be affected.

Study Design and Period: Cross sectional, observational study over 5 years

3. STUDY DESIGN

Cross sectional observational study
Study Population: 60 apparently healthy athletes and 60 apparently healthy non-athletes.

Controls: The control population will consist of 60 sex and aged matched healthy athletes with normal QRS complexes (paired for the athlete group with low QRS complexes) and 60 non athletes (paired for the non-athlete group with low QRS complexes).

Study duration: 60 months

3.1. STUDY OUTCOME MEASURES

Primary outcomes: 1. Prevalence of low QRS voltages in athletes and young non-athletic population on ECG analysis. **2.** Prevalence of myocardial fibrosis in the young athletic and non-athletic population with low QRS.

Exploratory secondary outcomes: 3. The proportion of individuals with low QRS complexes and myocardial fibrosis with rare protein altering variant in a cardiomyopathy gene. **4.** Exercise related ventricular premature beats or a ventricular premature beat burden of > 500 beats on a Holter monitor.

PLANNED SUBGROUP ANALYSIS: We will investigate whether concomitant exercise related ventricular premature beats or a ventricular premature beat burden of > 500 beats on a Holter monitor predict myocardial fibrosis in athletes and non-athletes with low QRS complexes**.**

4. PARTICIPANT ENTRY

4.1. PRE-REGISTRATION EVALUATIONS

12-lead ECG: A standard 12-lead ECG will be performed using either a MAC 5000 or MAC 5500 digital resting ECG recorder

Blood Test: A thyroid function test will be performed to ensure participants meet the inclusion criteria and do not have thyroid disease as a potential confounding factor to this study.

4.2. INCLUSION CRITERIA

Inclusion criteria: athletes and non-athletes with low QRS complexes who are asymptomatic and with a body mass index <30.

4.3. EXCLUSION CRITERIA

Exclusion Criteria for Controls and Athletes: Individuals with cardiac symptoms; past medical history of cardiac disease; family history of SCD <40 years old or cardiomyopathy; previous myocarditis; lung disease; individuals with pacemakers, defibrillators; pregnant women; advanced kidney and/or liver disease; no known thyroid disease, T-wave inversion or other training unrelated ECG changes, significant valvular heart disease or intra-cardiac shunt on echocardiography.

4.4. WITHDRAWAL CRITERIA

Study participants can decide to withdraw from the study at any point

5. ADVERSE EVENTS

5.1. DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*

- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2. REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs

All such events, whether expected or not, should be recorded- it should be specified if only some non-serious AEs will be recorded, any reporting should be consistent with the purpose of the trial end points.

5.3.2 Serious AEs

An SAE form should be completed and emailed to the Chief Investigator within 24 hours. However, relapse and death due to an pre-existing condition, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to Dr Sabiha Gati where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.
Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
RGIT@imperial.ac.uk
CI email (and contact details below)
S.gati@rbht.nhs.uk
Fax: N/A
Please send SAE forms to: lowQRS@rbht.nhs.uk
Tel: 07977 352296 (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

Participants who require ongoing clinical surveillance will be followed up in the specialist services at Royal Brompton Hospital. Individuals living afar will be referred to their primary care physician to instigate a formal referral to the relevant local specialist clinic.

Any relevant incidental findings on the cardiac MRI that is directly not related to the heart would be referred to the primary care physician for appropriate investigations and onward referral if required.

LOSS TO FOLLOW UP: To minimise loss to attendance there will be telephone and written communication during and after investigation. NHS details will be obtained from athletes so that GPs can be contacted for up-to-date details should participants be uncontactable.

END OF THE STUDY: The study will be completed following completion of all investigations as outlined in the study protocol, availability and analysis of data including genetic results on all 240 subjects (120 athletes and 120 young individuals). The pre-planned date for completion is 30 November 2025.

7. STATISTICS AND DATA ANALYSIS

The study to contain 240 participants as per the power calculation below.

POWER CALCULATION:

Athletes: Given a 4% prevalence of low QRS complexes in athletes[28] a sample of 2,500 athletes' ECGs would be expected to yield 100 cases of athletes with low QRS. In a study by Zorzi et al[4], 20% of athletes with myocardial fibrosis exhibited low QRS complexes in the limb leads, while the athletes with normal QRS had no myocardial fibrosis. Based on these parameters, for a power of 90% and 5% significance, a sample size of 55 athletes with low QRS complexes and 55 athletes with normal QRS is required to detect a difference in proportion of myocardial fibrosis. Allowing for a 5% exclusion rate following eligibility, we will recruit 60 athletes with and 60 athletes without low QRS complexes for further investigations.

Young Population: Given a 2% prevalence of low QRS complexes in the general population and taking into consideration that 36.5% of the UK population is young (aged 14-44 years old), a review of 12,000 young individuals' ECGs would be expected to yield 88 cases with low QRS. Again, using the study by Zorzi et al[4], and assuming these parameters to hold in the general population of young people, for a power of 90% and 5% significance, a sample size of 55 young people with low QRS complexes and 55 young people with normal QRS is required to detect a difference in proportion of scar. Allowing for a 5% exclusion rate following eligibility, we will recruit 60 young people with and 60 young people without low QRS complexes for further investigations.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

8.1. ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the Central London Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2. CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3. CONFIDENTIALITY

Collection, storage and assessment of participant data will abide by the GMC good medical practice guide and general data protection regulation (GDPR). Case Report Forms (CRF) will be designed by the chief investigator (CI). Required data will be put on the project database under patients pseudo-anonymised ID. Research staff will enter all research data onto a password protected excel spreadsheet. Only research team members will have access to this spreadsheet via data sharing agreements following patient consent. Master spreadsheet will be stored on secure servers in Royal Brompton Hospital. Consent Forms and patient ID log will be stored securely with the investigator site file at participating sites and will only be accessible to the research team. Original CRF with patient identifiable details will be stored in patients' medical records and clinical results will be stored as per standard hospital guidelines for investigations which are part of standard of care and will be kept confidential. The Hospital PACS system will store all CMR images in line with hospital protocols. All genetic data will be stored on the Imperial college HPC and in line with Imperial College FoM policies for storage and publication of genetic data from human subjects. All information will be de-identified, but with linked IDs. We will comply with the Hospital and University policies on managing confidentiality and data security and consult with the Hospital and College's Joint Research Compliance Office to ensure that only robustly anonymised data will be made publicly available, and all data sharing activities comply with GDPR.

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Data will be pseudo-anonymised.

8.4. INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5. SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6. FUNDING

Cardiac Risk in the young charitable organisation is funding this study.

8.7. AUDITS

The study may be subject to audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Dr Nirmitha Jayaratne - Clinical Research fellow to Dr Sabiha Gati.

10. PUBLICATION POLICY

It is expected that all parties involved in the publication of content in any specific journal (the publisher, editors, authors, and reviewers) will follow the guidelines on best practice and publication ethics based on the journal policy. The Journal to which the manuscript will be submitted is committed to investigating cases of alleged editor, author, and reviewer misconduct arising from its activities, and will follow COPE Guidelines in all cases.

11. REFERENCES

1. Corrado D, van Tintelen PJ, McKenna WJ, Hauer RNW, Anastastakis A, Asimaki A, Basso C, Bauce B, Brunckhorst C, Bucciarelli-Ducci C, Duru F, Elliott P, Hamilton RM, Haugaa KH, James CA, Judge D, Link MS, Marchlinski FE, Mazzanti A, Mestroni L, Pantazis A, Pelliccia A, Marra MP, Pilichou K, Platonov PGA, Protonotarios A, Rampazzo A, Saffitz JE, Saguner AM, Schmied C, Sharma S, Tandri H, Te Riele ASJM, Thiene G, Tsatsopoulou A, Zareba W, Zorzi A, Wichter T, Marcus FI, Calkins H. Arrhythmogenic right ventricular cardiomyopathy: evaluation of the current diagnostic criteria and differential diagnosis. *Eur Heart J*. 2019;Available from: https://doi.org/10.1093/eurheartj/ehz669
2. Usoro AO, Bradford N, Shah AJ, Soliman EZ. Risk of mortality in individuals with low QRS voltage and free of cardiovascular disease. *Am J Cardiol*. 2014;113:1514–1517.
3. Finocchiaro G, Papadakis M, Robertus J-L, Dhutia H, Steriotis AK, Tome M, Mellor G, Merghani A, Malhotra A, Behr E, Sharma S, Sheppard MN. Etiology of Sudden Death in Sports: Insights From a United Kingdom Regional Registry. *J Am Coll Cardiol*. 2016;67:2108–2115.
4. Zorzi A, Perazzolo Marra M, Rigato I, De Lazzari M, Susana A, Niero A, Pilichou K, Migliore F, Rizzo S, Giorgi B, De Conti G, Sarto P, Serratosa L, Patrizi G, De Maria E, Pelliccia A, Basso C, Schiavon M, Bauce B, Iliceto S, Thiene G, Corrado D. Nonischemic Left Ventricular Scar as a Substrate of Life-Threatening Ventricular Arrhythmias and Sudden Cardiac Death in Competitive Athletes. *Circ Arrhythm Electrophysiol*. 2016;9.
5. Zorzi A, Bettella N, Tatangelo M, Del Monte A, Vessella T, Poscolieri B, Crescenzi C, Pegorin D, D'Ascenzi F, Pescatore V, Giada F, Sarto P, Calò L, Schiavon M, Gregori D, Hadley DM, Drezner JA, Pelliccia A, Corrado D. Prevalence and clinical significance of isolated low QRS voltages in young athletes. *Eur Eur pacing, arrhythmias, Card Electrophysiol J Work groups Card pacing, arrhythmias, Card Cell*

Electrophysiol Eur Soc Cardiol. 2022;
6. Chinitz JS, Cooper JM, Verdino RJ. Electrocardiogram voltage discordance: interpretation of low QRS voltage only in the limb leads. *J Electrocardiol*. 2008;41:281–286.
7. Madias JE. Low QRS voltage and its causes. *J Electrocardiol*. 2008;41:498–500.
8. Fraley MA, Birchem JA, Senkottaiyan N, Alpert MA. Obesity and the electrocardiogram. *Obes Rev*. 2005;6:275–281.
9. Alpert MA, Terry BE, Cohen M V, Fan TM, Painter JA, Massey C V. The electrocardiogram in morbid obesity. *Am J Cardiol*. 2000;85:908–10, A10.
10. Bruch C, Schmermund A, Dagres N, Bartel T, Caspari G, Sack S, Erbel R. Changes in QRS voltage in cardiac tamponade and pericardial effusion: reversibility after pericardiocentesis and after anti-inflammatory drug treatment. *J Am Coll Cardiol*. 2001;38:219–226.
11. Casale PN, Devereux RB, Kligfield P, Eisenberg RR, Phillips MC. Pericardial effusion: relation of clinical echocardiographic and electrocardiographic findings. *J Electrocardiol*. 1984;17:115–121.
12. Eisenberg MJ, de Romeral LM, Heidenreich PA, Schiller NB, Evans GTJ. The diagnosis of pericardial effusion and cardiac tamponade by 12-lead ECG. A technology assessment. *Chest*. 1996;110:318–324.
13. Hamer JP, Janssen S, van Rijswijk MH, Lie KI. Amyloid cardiomyopathy in systemic non-hereditary amyloidosis. Clinical, echocardiographic and electrocardiographic findings in 30 patients with AA and 24 patients with AL amyloidosis. *Eur Heart J*. 1992;13:623–627.
14. Madias JE. Transient attenuation of the amplitude of the QRS complexes in the diagnosis of Takotsubo syndrome. *Eur Hear journal Acute Cardiovasc care*. 2014;3:28–36.
15. Madias JE, Agarwal H, Win M, Medepalli L. Effect of weight loss in congestive heart failure from idiopathic dilated cardiomyopathy on electrocardiographic QRS voltage. *Am J Cardiol*. 2002;89:86–88.
16. Oliver C, Marin F, Pineda J, Lujan J, Climent VE, Garcia A, Arrarte V, Sogorb F. Low QRS voltage in cardiac tamponade: a study of 70 cases. Int. J. Cardiol. 2002;83:91–92.
17. Parameswaran R, Maniet AR, Goldberg SE, Goldberg H. Low electrocardiographic voltage in pericardial effusion. *Chest*. 1984;85:631–634.
18. Pinamonti B, Dreas L, Bussani R, Mestroni L, Silvestri F, Tanganelli P, Camerini F. [Cardiac amyloidosis. Invasive and noninvasive diagnosis]. *G Ital Cardiol*. 1987;17:1016–1030.
19. Rodman DM, Lowenstein SR, Rodman T. The electrocardiogram in chronic obstructive pulmonary disease. *J Emerg Med*. 1990;8:607–615.
20. Sorbello A, Giudice JC, Papa LA. The relationship of low voltage on the electrocardiogram and chronic obstructive pulmonary disease. *Clin Cardiol*. 1982;5:657–660.
21. Harmon KG, Asif IM, Klossner D, Drezner JA. Incidence of sudden cardiac death in National Collegiate Athletic Association athletes. *Circulation*. 2011;123:1594–1600.
22. Harmon KG, Asif IM, Maleszewski JJ, Owens DS, Prutkin JM, Salerno JC, Zigman ML, Ellenbogen R, Rao AL, Ackerman MJ, Drezner JA. Incidence, Cause, and Comparative Frequency of Sudden Cardiac Death in National Collegiate Athletic Association Athletes: A Decade in Review. *Circulation*. 2015;132:10–19.
23. Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980-2006. *Circulation*. 2009;119:1085–1092.
24. Sharma S, Drezner JA, Baggish A, Papadakis M, Wilson MG, Prutkin JM, La Gerche

A, Ackerman MJ, Borjesson M, Salerno JC, Asif IM, Owens DS, Chung EH, Emery MS, Froelicher VF, Heidbuchel H, Adamuz C, Asplund CA, Cohen G, Harmon KG, Marek JC, Molossi S, Niebauer J, Pelto HF, Perez M V, Riding NR, Saarel T, Schmied CM, Shipon DM, Stein R, Vetter VL, Pelliccia A, Corrado D. International recommendations for electrocardiographic interpretation in athletes. *Eur Heart J*. 2018;39:1466–1480.

25. Corrado D, Pelliccia A, Heidbuchel H, Sharma S, Link M, Basso C, Biffi A, Buja G, Delise P, Gussac I, Anastasakis A, Borjesson M, Bjørnstad HH, Carrè F, Deligiannis A, Dugmore D, Fagard R, Hoogsteen J, Mellwig KP, Panhuyzen-Goedkoop N, Solberg E, Vanhees L, Drezner J, Estes N a M, Iliceto S, Maron BJ, Peidro R, Schwartz PJ, Stein R, Thiene G, Zeppilli P, McKenna WJ. Recommendations for interpretation of 12-lead electrocardiogram in the athlete. *Eur Heart J*. 2010;31:243–59.
26. Uberoi A, Stein R, Perez M V, Freeman J, Wheeler M, Dewey F, Peidro R, Hadley D, Drezner J, Sharma S, Pelliccia A, Corrado D, Niebauer J, Estes NAM 3rd, Ashley E, Froelicher V. Interpretation of the electrocardiogram of young athletes. *Circulation*. 2011;124:746–757.
27. Drezner JA, Sharma S, Baggish A, Papadakis M, Wilson MG, Prutkin JM, Gerche A La, Ackerman MJ, Borjesson M, Salerno JC, Asif IM, Owens DS, Chung EH, Emery MS, Froelicher VF, Heidbuchel H, Adamuz C, Asplund CA, Cohen G, Harmon KG, Marek JC, Molossi S, Niebauer J, Pelto HF, Perez M V, Riding NR, Saarel T, Schmied CM, Shipon DM, Stein R, Vetter VL, Pelliccia A, Corrado D. International criteria for electrocardiographic interpretation in athletes: Consensus statement. *Br J Sports Med*. 2017;51:704 LP – 731.
28. Mango F, Caselli S, Luchetti A, Pelliccia A. Low QRS voltages in Olympic athletes: Prevalence and clinical correlates. *Eur J Prev Cardiol*. 2020;2047487320914758.
29. Rawlins J, Carre F, Kervio G, Papadakis M, Chandra N, Edwards C, Whyte GP, Sharma S. Ethnic differences in physiological cardiac adaptation to intense physical exercise in highly trained female athletes. *Circulation*. 2010 [cited 2010 Sep 8];121:1078–85.
30. Halliday BP, Gulati A, Ali A, Guha K, Newsome S, Arzanauskaite M, Vassiliou VS, Lota A, Izgi C, Tayal U, Khalique Z, Stirrat C, Auger D, Pareek N, Ismail TF, Rosen SD, Vazir A, Alpendurada F, Gregson J, Frenneaux MP, Cowie MR, Cleland JGF, Cook SA, Pennell DJ, Prasad SK. Association Between Midwall Late Gadolinium Enhancement and Sudden Cardiac Death in Patients With Dilated Cardiomyopathy and Mild and Moderate Left Ventricular Systolic Dysfunction. *Circulation*. 2017;135:2106–2115.
31. Monserrat L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. *J Am Coll Cardiol*. 2003;42:873–879.
32. Biffi A, Pelliccia A, Verdile L, Fernando F, Spataro A, Caselli S, Santini M, Maron BJ. Long-term clinical significance of frequent and complex ventricular tachyarrhythmias in trained athletes. *J Am Coll Cardiol*. 2002;40:446–452.
33. James CA, Jongbloed JDH, Hershberger RE, Morales A, Judge DP, Syrris P, Pilichou K, Domingo AM, Murray B, Cadrin-Tourigny J, Lekanne Deprez R, Celeghin R, Protonotarios A, Asatryan B, Brown E, Jordan E, McGlaughon J, Thaxton C, Kurtz CL, van Tintelen JP. International Evidence Based Reappraisal of Genes Associated With Arrhythmogenic Right Ventricular Cardiomyopathy Using the Clinical Genome Resource Framework. *Circ Genomic Precis Med*. 2021;14:e003273.
34. Jordan E, Peterson L, Ai T, Asatryan B, Bronicki L, Brown E, Celeghin R, Edwards M, Fan J, Ingles J, James CA, Jarinova O, Johnson R, Judge DP, Lahrouchi N, Lekanne Deprez RH, Lumbers RT, Mazzarotto F, Medeiros Domingo A, Miller RL, Morales A,

Murray B, Peters S, Pilichou K, Protonotarios A, Semsarian C, Shah P, Syrris P, Thaxton C, van Tintelen JP, Walsh R, Wang J, Ware J, Hershberger RE. Evidence-Based Assessment of Genes in Dilated Cardiomyopathy. *Circulation*. 2021;144:7–19.

35. Harmon KG, Drezner JA, Wilson MG, Sharma S. Incidence of sudden cardiac death in athletes: a state-of-the-art review. *Heart*. 2014;100:1227–1234.

Appendix 1. Summary of investigations, treatment and assessments

Recruitment (48 months)			
Athletes' ECGs	**= 2500**	**Young population ECGs**	**= 12,000**
Athletes with low QRS	**60**	**Young population with low QRS**	**60**
Athletes with Normal ECGs	**60**	**Young population with Normal ECGs**	**60**

↓

Consent
Appointment Date
Online booking system for appointments for 30 days

↓

Testing at Royal Brompton Hospital (One-Stop-Shop)			
Blood test: TFTs	**CMR**	**Exercise testing/CPET**	**24-Hour Holter**

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Results Reporting (2-weeks)	
Patient letter summarising tests results	**GP letter communicating and advising on abnormal findings**

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Athletes with and without low QRS and myocardial fibrosis	**Young population with and without low QRS and myocardial fibrosis**
Genetic Testing for DCM/AVC Panel	
N= 25	**N=25**

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Genetic Results Reporting (6 months)

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Statistical analysis of results and write-up (12 months)