Institution: Liverpool John Moores University

Unit of Assessment: 26

Title of case study:

"Cardiovascular deaths in young athletes - Preventing the tragedy": The development and implementation of evidence-based pre-participation cardiovascular screening protocols

1. Summary of the impact:

There are twelve young (<35 years) sudden cardiac deaths each week in the UK. These deaths in the young, fit and otherwise healthy are devastating, result in significant life-years lost and can lead to substantial media attention. The focus of this case study is based on the fact that the majority of these deaths may be preventable as it is possible to detect young athletes at risk of sudden cardiac death through pre-participation cardiovascular screening (PPS). The Cardiovascular Health Sciences Group (CHS) within the Research Institute for Sport and Exercise Sciences (RISES) has a long history of novel empirical research in this field that has had significant and far-reaching impact by; a) determining UK-based pathology data in cases of sudden cardiac death that led to the establishment of a National Register for these cases, b) contributing to international consensus statements (e.g. European Society of Cardiology) related to PPS that have been adopted by major sporting teams and organisations (e.g. Liverpool FC), c) the production of evidence-based screening policy guidelines for PPS (e.g. Cardiac Risk in the Young [CRY], British Society of Echocardiography), and d) the establishment of PPS screening activity in Liverpool (e.g. CRY clinic; elite athletes) and internationally (e.g. ASPETAR, Qatar). Our work has made a significant contribution to improving the cardiovascular care of athletes in the UK and globally.

2. Underpinning research:

By way of context, the CHS group within RISES has published one of the largest series of papers characterising the upper physiological limits of cardiac adaptation in adolescent and adult athletes. This work has been undertaken by the following staff; Professor Greg Whyte (GW; 2006-present), Professor Keith George (KG; 2002-present), Professor Tim Cable (TC; 1993-present), Professor Daniel Green (DG; 2006-present) and Reader Dr David Oxborough (DO; 2012-present) in conjunction with multiple collaborators within the UK and around the globe.

The CHS group, in collaboration with the National Centre of Excellence for Cardiac Pathology, located at St. George's Hospital, published the first UK study to systematically examine the aetiology of sudden cardiac death in 118 young sudden cardiac death victims **(Sec.2, Ref.1).** The results of this study confirmed the importance of cardiomyopathies in the aetiology of sudden cardiac deaths in young athletes in the UK. This work also highlighted that the hearts of these victims were often morphologically normal, a finding that has two consequences; 1) this implicates the importance of electrical disorders (e.g. ionchannelopathies) in the incidence of sudden cardiac death in this cohort, and 2) it reinforces the issue that there is substantial phenotypical overlap (the "Grey Zone") between pathology and physiological adaptation that requires careful evidence-based PPS protocols and criteria.

In developing sustained links with sports governing bodies, charities and clinical groups, the CHS has published novel empirical work related to the upper normal limits of the athletic heart phenotype. This has been undertaken in association with the key investigative tools associated with PPS, namely ECG and echocardiography. For example, the CRG has published a series of papers examining the ECG in large cohorts of elite athletes. These papers included the largest studies of their kind examining in excess of 2,000 elite athletes including unique data across gender and ethnicity **(Sec.3, Ref.2)**, that specifically reported a 0.4% prevalence of long-QT syndrome and established new upper limits for QT interval in elite athletes of 500 ms.

In addition, the CHS group has published a series of studies describing the upper normal

(physiological) limits for the morphological characteristics of the left ventricle, right ventricle and left atrium in a range of elite athletic populations (**Sec.3, Ref.3-5**). Specifically, data (**Sec.3, Ref.3**) in a large group of elite endurance athletes provided upper normal limits for right ventricular size demonstrating unique right ventricular enlargement that is different to that observed in arrhythmogenic right ventricular cardiomyopathy that has been implicated in a significant number of athletic sudden cardiac deaths in the UK and globally. Uniquely, this paper also described novel indices of regional and global right ventricular function as well as assessing the impact of cardiac size upon function. This work provides supporting evidence for the application of novel echocardiographic indices in PPS allowing further improvement in the differentiation of physiological versus pathological adaptation. The impact of ethnicity on sudden cardiac death data has been noted globally. Characterisation of the effect of ethnicity on the athlete's heart, however, was required to improve PPS. The CHS were the first to publish, with key collaborators, comparative echocardiographic data in Caucasian, Afro-Caribbean and West-Asian athletes including gender comparisons. For example, we published the first data characterising cardiac morphology in a large sample of elite black athletes in comparison with elite Caucasian athletes (**Sec.3, Ref.4**). The key outcome was the significantly higher prevalence of black athletes (18% vs. 4%) presenting with left ventricular wall thickness above the normal upper limit (>12 mm). Furthermore, 3% of black athletes exhibited left ventricular wall thickness above the accepted elite athlete upper normal limit for white athletes ($\geq$15 mm), that would trigger further investigation. In a follow-up study (**Sec.3, Ref.5**) we highlighted similar right ventricular adaptations across ethnic groups which serves as valuable information for PPS when ECG findings are more likely to be 'abnormal' in athletes of Afro-Caribbean ethnicity.

3. References to the research:

Reference for the peer-reviewed outputs from the RISES research described in Section 2.

1. de Noronha SV, Sharma S, Papadakis M, Desai S, Whyte G, Sheppard MN. Aetiology of sudden cardiac death in athletes in the United Kingdom: a pathological study. *Heart.* 2009 Sep;95(17):1409-14. doi: 10.1136/hrt.2009.168369.

2. Basavarajaiah, S., Wilson, M., Whyte, G., Shah, A., Behr, E. and Sharma, S. Prevalence and Significance of an Isolated Long QT Interval in Elite Athletes *European Heart Journal* 2007;28(23):2944-2949. doi: 10.1093/eurheartj/ehm404.

3. Oxborough, D., Sharma, S., Shave, R., Whyte, G., Birch, K., Artis, N., Batterham, A. and George, K. The Right Ventricle of the Endurance Athlete: The Relationship between Morphology and Deformation. *Journal of the American Society of Echocardiography* 2012; 25:263-271. doi: 10.1016/j.echo.2011.11.017.

4. Basavarajaiah S, Boraita A, Whyte G, Wilson M, Carby L, Shah A, Sharma S. Ethnic differences in left ventricular remodelling in highly-trained athletes relevance to differentiating physiologic left ventricular hypertrophy from hypertrophic cardiomyopathy. J Am Coll Cardiol. 2008 Jun 10;51(23):2256-62. doi: 10.1016/j.jacc.2007.12.061.

5. Zaidi, A., Saqib G., Sharma, R., Oxborough, D., Panoulas, V., Sheikh, N., Gati, S., Papadakis, M. and Sharma, S. Physiological Right Ventricular Adaptation in Elite Athletes of African and Afro-Caribbean Origin: Clinical Perspective. *Circulation.* 2013;127:1783-1792. doi: 10.1161/CIRCULTAIONAHA.112.000270.

All the research papers underwent peer-review before being published in high quality, international journals.

4. Details of the impact:

With the aim of linking research to impact, members of the CHS group have engaged in strategic and high profile dissemination activity. Notably this has involved organising (GW), chairing (GW) and

presenting (DO/KG/GW/TC) at the annual Cardiac Risk in the Young International conference in Sports Cardiology (2006-present) where the latest evidence-based practice related to PPS is presented to clinicians and discussed. Other dissemination events have occurred at the British Cardiovascular Society, Institute of Sport and Exercise Medicine, the British Society of Echocardiography as well as to sports governing bodies (UK Sport High Performance conference, English FA, Irish Institute of Sport). Internationally, symposia, debates and round table discussions have been conducted at the European College of Sports Sciences, American College of Sports Medicine, Canadian Exercise Physiology, International Conference on Science and Education and Medicine in Sports, the IOC Sports Medicine Conference and the ASPETAR Conference on the Cardiac Screening of Athletes. The latter event led to the translation of CHS research via the development of a PPS programme in Qatar.

Research work by CHS staff (**Sec.3, Ref.1**) was instrumental, alongside the charity Cardiac Risk in the Young, in the establishment in 2010 of the UK's first national registry of sudden cardiac deaths at the National Centre of Excellence for Cardiac Pathology at St George's Hospital (**Sec.5, Source.A**). This now provides UK-specific data related to the incidence and aetiology of sudden cardiac death in the young in the UK which provides support for on-going developments in PPS, diagnosis and treatment. This has also enhanced the quality of care for families affected by a young sudden cardiac death by providing a fast-track to specialist diagnostics.

A major impact of CHS research is that it has resulted in significant changes to the decision making criteria/algorithm[s] employed in PPS in the UK, Europe and across the world through the production of consensus statement documents (**Sec.5, Source.B/C**). Consensus statements are a standard method of changing practice and clinical decision marking and have global reach. Advancements in practice include updated diagnostic algorithms (*i.e.* ECG criteria) for cardiologists and clinical scientists and include CHS work on long QT syndrome (**Sec.3, Ref.2**). These data were adopted in the European Cardiology Society consensus statement for ECG interpretation in athletes (**Sec.5, Source.B**) as well as the consequent inclusion in the recent Seattle Criteria (**Sec.5, Source.C**) for PPS. These consensus guidelines, including the work produced by the CHS, have become the cornerstone of PPS globally and have been adopted by influential sports governing bodies (e.g. IOC, FIFA, Union International du Cycling).

Research from the CHS have helped to characterise the structural and functional phenotype of the athlete's heart (**Sec.3, Ref.3-5**) and these represent the current 'gold standard' in relation to upper normal physiologic limits of cardiac adaptation, across gender and ethnicity for all sporting populations. These data, and other CHS publications, have directly contributed to bespoke educational material and practice guidelines for PPS in the UK. Specifically, two "Guideline" documents have been produced by the British Society of Echocardiography and endorsed by the charity CRY (**Sec.5, Source.D/E**) and have now changed the PPS of athletes in the UK. To date these guidelines have been disseminated to over 4000 UK and international members of the British Society of Echocardiography and systematically enhanced service delivery in all clinical echocardiography departments in the UK (**Sec.5, Source.F**).

CHS staff, in association with CRY, launched a "CRY Cardiovascular Screening Centre" at LJMU opened by the then Secretary of State Rt. Hon Andrew Burnham in 2009. This centre has provided a direct access service for young people and athletes in the local community and since its establishment has provided cardiac sports screening to over 200 young people (**Sec.5, Source.A**). The CHS group, in collaboration with clinical colleagues, have extended this service to elite athlete groups. Specifically, this has led to a comprehensive PPS programme for Liverpool FC (2010-present). To date we have completed PPS in over 500 young athletes, with approximately 10% being referred on for further investigation and monitoring and one professional athlete has been removed from competitive sport due to the detection of cardiovascular pathology and increased risk for sudden cardiac death (**Sec.5, Source.G**). The translation of CHS research and development of a large scale PPS program has also occurred within the National Sports Medicine and Orthopaedic Hospital (ASPETAR), Doha, Qatar (Qatar National Pre-participation Screening Programme launched in 2009). This programme has now screened 6730 athletes with 12 cases of hypertrophic cardiomyopathy detected (11 athletes disqualified from competition) as well as 22 other pathological

conditions resulting in disqualification or on-going monitoring. This process has also provided new normative data for ECG and echocardiographic parameters in Arabic/Asian athletes to further feedback into diagnostic criteria and treatment planning (**Sec.5, Corr.H**).

The provision of improved evidence-based guidelines for PPS has changed policy and PPS implementation in the UK and globally. The Chair of the IOC Medical Commission has stated (2013) *"The CHS group's on-going research, leading to the continual enhancement of screening guidelines, has improved sensitivity and specificity of diagnosis and resulted in an improved quality of care for athletes across the globe"* (**Sec.5, Source.I**).

5. Sources to corroborate the impact:

External Source to Corroborate Impact	Nature of Evidence
A. Director of the CRY Centre of Inherited Cardiovascular Disease and Sports Cardiology, St George's Hospital.	Uptake of research development of National Registry of Sudden Cardiac Deaths. Corroboration of launch and impact of the CRY Cardiovascular Screening Centre at LJMU.
B. Corrado D *et al.* Section of Sports Cardiology, European Association of Cardiovascular Prevention and Rehabilitation. Recommendations for interpretation of 12-lead electrocardiogram in the athlete. *Eur Heart J.* 2010;31(2):243-59.	Impact of research on European Society of Cardiology Consensus statement on ECG interpretation in PPS.
C. Drezner JA *et al.* Electrocardiographic interpretation in athletes: the 'Seattle Criteria'. Br J Sports Med. 2013;47(3):122-4.	Translation of research from ECS consensus statement to the Seattle Criteria for interpretation of ECG in PPS.
D. The Echocardiographic Assessment of the Right Ventricle with particular reference to Arrhythmogenic Right Ventricular Cardiomyopathy. A Protocol of the British Society of Echocardiography. May 2013	Research informed policy statement and practical guidelines for clinicians involved in PPS of young athletes.
E. A Guideline for the practice of echocardiography in the cardiovascular screening of sports participants. *A Joint Policy Statement of the British Society of Echocardiography and Cardiac risk in the Young.* June 2013	Research informed policy statement and practical guidelines for clinicians involved in PPS of young athletes.
F. President of the British Society of Echocardiography	Link between RISES Research and BSE Educational Committee work and the national and international reach of BSE policy documents.
G. Consultant Cardiologist, Countess of Chester Hospital and Cardiac Screening Lead at Liverpool Football Club	The role of RISES research in PPS in elite athletes in the UK, specifically Liverpool FC.
H. Research Manager and Cardiac Screening Lead, Aspetar, Qatar Orthopaedic and Sports Medicine Hospital	The role of RISES research and CRG staff in driving international PPS in elite athletes and follow up details of tests and implications for athletes health.
I. Director of Medicine, International Olympic Committee	Corroboration of the uptake of RISES research and impact on PPS screening and healthcare of athletes in elite sport.