ESC European Society of Cardiology
European Heart Journal (2022) **00**, 1–5
https://doi.org/10.1093/eurheartj/ehac043
CARDIOPULSE

Global Spotlights

800 years of research at the University of Padua (1222–2022): contemporary insights into Sports Cardiology

Domenico Corrado *, Alessandro Zorzi , Cristina Basso , and Gaetano Thiene

Inherited Cardiomyopathy and Sports Cardiology Unit and Cardiovascular Pathology Unit, Department of Cardiac, Thoracic, and Vascular Sciences and Public Health, University of Padova Medical School, Via Giustiniani 2, 35128, Padova, Italy

Holding a long tradition of excellence since 1222, the University of Padua is one of the oldest and most prestigious academic centres in Europe. In the 16th–17th centuries, milestone achievements from Padua's researchers in astronomy, medicine, and natural philosophy contributed to the cultural and scientific development of humanity.[1] Distinguished teachers and alumni of the University of Padua include Nicolaus Copernicus (1473–1543), Galileo Galilei (1564–1642), Andreas Vesalius (1514–62), William Harvey (1578–1657), and Gian Battista Morgagni (1682–1771) (*Figure 1*). On the anniversary of 800 years (1222–2022) of research and teaching at the University of Padua, we are taking the opportunity to briefly review the contemporary insights into Sports Cardiology provided by the Padua research team over the last 50 years.

Sports Cardiology is a new and rapidly evolving cardiological subspeciality, whose main objectives are the evaluation of the effects of regular exercise on the heart (athlete's heart) and the assessment of sports-related cardiovascular risks, with particular reference to concealed diseases that may predispose athletes to sudden cardiac death (SCD). Sports Cardiology has the task of designing and implementing preventive strategies, mostly relying on pre-participation cardiovascular screening aimed to identify at-risk athletes. The Padua research team has substantially contributed to setting the scientific basis of the Sports Cardiology discipline by identifying the heart diseases underlying fatalities during sport performance, and by promoting the implementation of screening programmes to reduce the cardiovascular risk of European athletes.

It all started in 1979, when a systematic clinico-pathological investigation on SCD occurring among young people and athletes (age ≤35 years) of the Veneto region of northeastern Italy was carried out by an interdisciplinary group of pathologists and cardiologists from the University of Padua. All SCD victims underwent a detailed post-mortem pathological examination of the heart, an evaluation of circumstances surrounding the fatal cardiac arrest, previous clinical history, electrocardiogram (ECG), and other clinical data that were correlated with the heart disease found at autopsy. The results of the University of Padua's investigation contributed to resolving the dilemma of cardiac arrest occurring suddenly and unexpectedly in young athletes who are apparently healthy and achieve extraordinary exercise performance without complaining of any symptoms. Clinical and pathologic findings showed that sports-related SCD victims had an underlying cardiovascular disorder, often clinically silent but predisposing to a sudden electrical instability of the heart.[2,3] Among these heart diseases, we identified a previously unreported cause of SCD in the athlete characterized by fibro-fatty replacement of the right ventricular myocardium then named 'arrhythmogenic right ventricular cardiomyopathy' (*Figure 2*, left panel). In 1988, an article on the subject was accepted for publication by the *New England Journal of Medicine*, providing the editor with detailed clinical data and pathologic illustrations case by case to overcome the skepticism raised by the novelty of the report.[2] Please note: since 1979, the heart specimens of all SCD victims have been painstakingly stored allowing for the retrieval and review of each case (*Figure 2*, right panel).

In 1996, the Padua research group began to collaborate with the local Centre for Sports Medicine to investigate the impact of systematic pre-participation ECG screening (mandated by law in Italy since 1982) on the prevention of SCD in young sports competitors. In 1998, another article in the *New England Journal of Medicine* reported the efficacy of the Italian screening programme in identifying athletes with hypertrophic cardiomyopathy, the leading cause of SCD in US

* Corresponding author. Tel: +39 0498 212 458, Email: domenico.corrado@unipd.it

Figure 1 Historic seats and celebrities of the University of Padova. (*A*) Palazzo del Bo (1493); (*B*) anatomical theatre (1594); (*C*) Nicolaus Copernicus (1473–1543), Polish astronomer; (*D*) Galileo Galilei (1564–1642), the father of modern science; (*E*) Andreas Vesalius (1514–62), founder of anatomy; (*F*) William Harvey (1578–1657), discoverer of blood circulation; (*G*) Gian Battista Morgagni (1682–1771), founder of pathological anatomy.

athletes.[4] We found that hypertrophic cardiomyopathy was an uncommon cause of fatal outcome in young Italian athletes undergoing systematic cardiovascular evaluation, which offered the possibility to identify at-risk athletes and protect them from the risk of SCD through disqualification.

A subsequent time-trend analysis of the incidence of SCD in young competitive athletes in the Veneto region between 1979 and 2004, published in *JAMA*, demonstrated a sharp decline of ≈90% in mortality rates among athletes after the introduction of the Italian screening programme in 1982, particularly because of fewer fatalities from cardiomyopathies.[5] By comparison, SCD rates did not change significantly over the study period among the unscreened sedentary population. Over the study periods, a parallel investigation of young athletes undergoing pre-participation cardiovascular evaluation at the Center for Sports Medicine in Padua demonstrated that the decline in mortality from cardiomyopathies was paralleled by the concomitant increase in the number of athletes with hypertrophic and arrhythmogenic right ventricular cardiomyopathy identified by the screening.[5] This study provided the most compelling evidence that ECG screening may save lives by identifying athletes with at-risk heart diseases.

The prevalence of false-positive findings at pre-participation screening depends largely on the criteria used to define an athlete's ECG as abnormal. The long-running experience with systematic ECG screening of Italian athletes offered the Padua research team the unique opportunity to characterize and report ECG abnormalities mostly associated with cardiovascular diseases at risk of SCD (*Figure 3*). In 2005, an European Society of Cardiology (ESC) study group coordinated by the Padua research team provided a common protocol of pre-participation screening for the prevention of SCD among European athletes using the ECG screening system in practice in Italy.[6] In 2010, a new perspective on the interpretation of an athlete's ECG was first provided by an ESC consensus document that was leaded by the Padua research team.[7] The document proposed modern criteria to distinguish 'physiologic' from 'pathologic' changes of the athlete's ECG. The original ESC criteria were refined by subsequent international consensus documents that further improved their diagnostic specificity to increase the cost-effectiveness of ECG screening.

In more recent years, there have been further contributions to Sports Cardiology from the continuous research of the Padua research team: (i) the identification of new substrates underlying cardiac arrest during sports, including non-ischaemic left ventricular scar and 'arrhythmic' mitral valve prolapse; (ii) the demonstration that serial (annual) cardiovascular evaluation increases by three times the screening sensitivity for inherited cardiomyopathies with late onset phenotype and acquired myocardial diseases, compared to screening once-only;[8] (iii) a better characterization of some ECG patterns, such as juvenile T-wave inversion, anterior T-wave inversion due to early repolarization, inferolateral T-wave inversion associated with papillary muscle hypertrophy, and low QRS voltages due to myocardial fibrosis; and (iv) diagnostic algorithm and risk

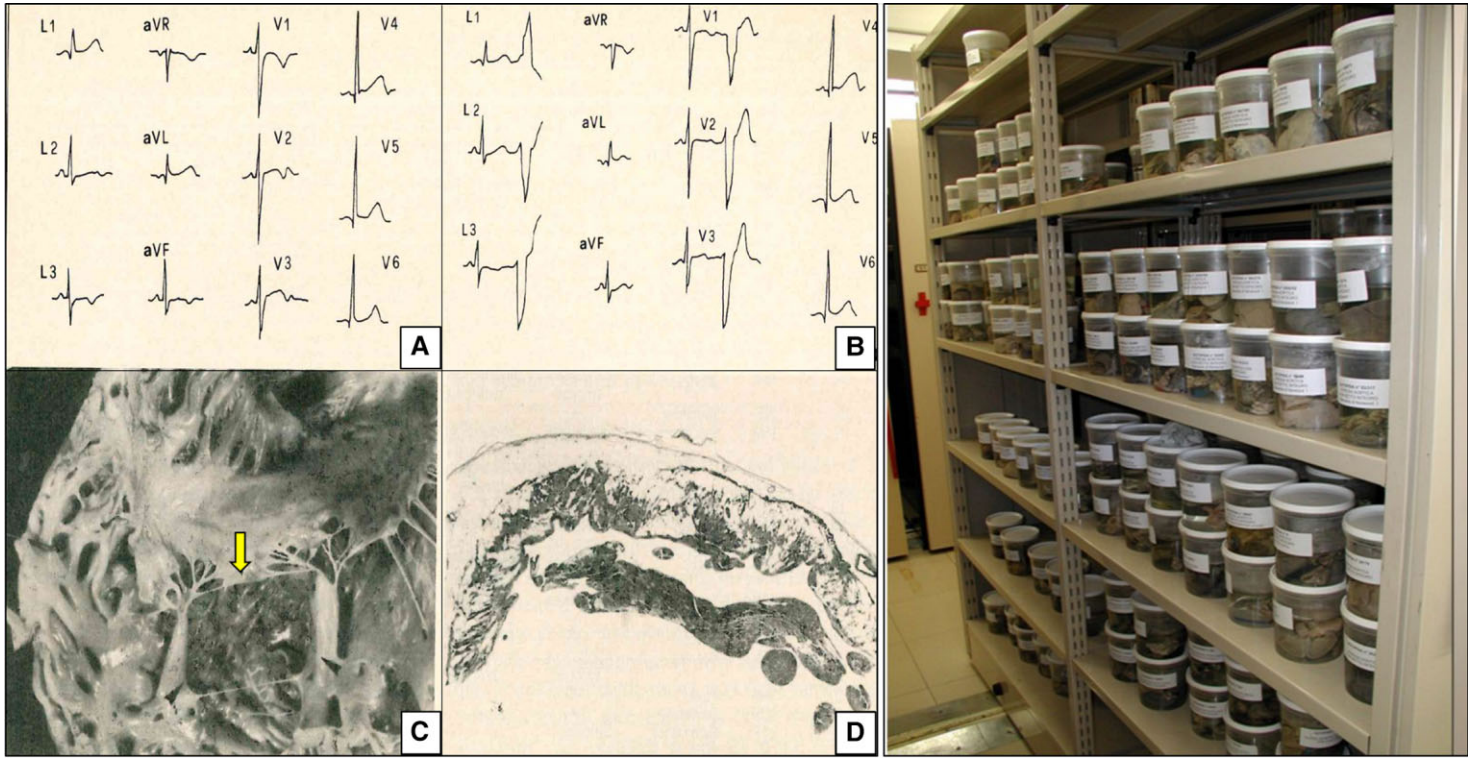

Figure 2 Left panel: A 16-year-old soccer player who died suddenly during a competitive match, who was one of the first reported athletes diagnosed with fatal arrhythmogenic right ventricular cardiomyopathy. (*A*) Basal electrocardiogram with T-wave inversion in inferior and right precordial leads; (*B*) premature ventricular beats with a left-bundle-branch-block morphology and superior QRS axis occurring during effort (Harvard-Montoye step test); (*C*) gross internal view of the inferior wall of the right ventricle showing scar with aneurysmal dilatation, just beneath the posterior leaflet of the tricuspid valve (arrow); (*D*) histology of the inferior wall of the right ventricle showing extensive fibro-fatty myocardial replacement. (Adapted with permission from Corrado *et al.* [3].) Right panel: Since 1979, the heart specimens of all young people and athletes, who died suddenly and were recorded in the registry of the University of Padua research programme, have been stored at the Institute of Pathological Anatomy and are available for re-examination, together with clinical records. This is a guaranty of the reliability of data on causes and trends of sudden cardiac death in young people and athletes in the Veneto Region of Italy, at odds with other reports that are mostly based on retrospective analysis of data from public media and insurance claims, which unavoidably led to mortality underestimation.

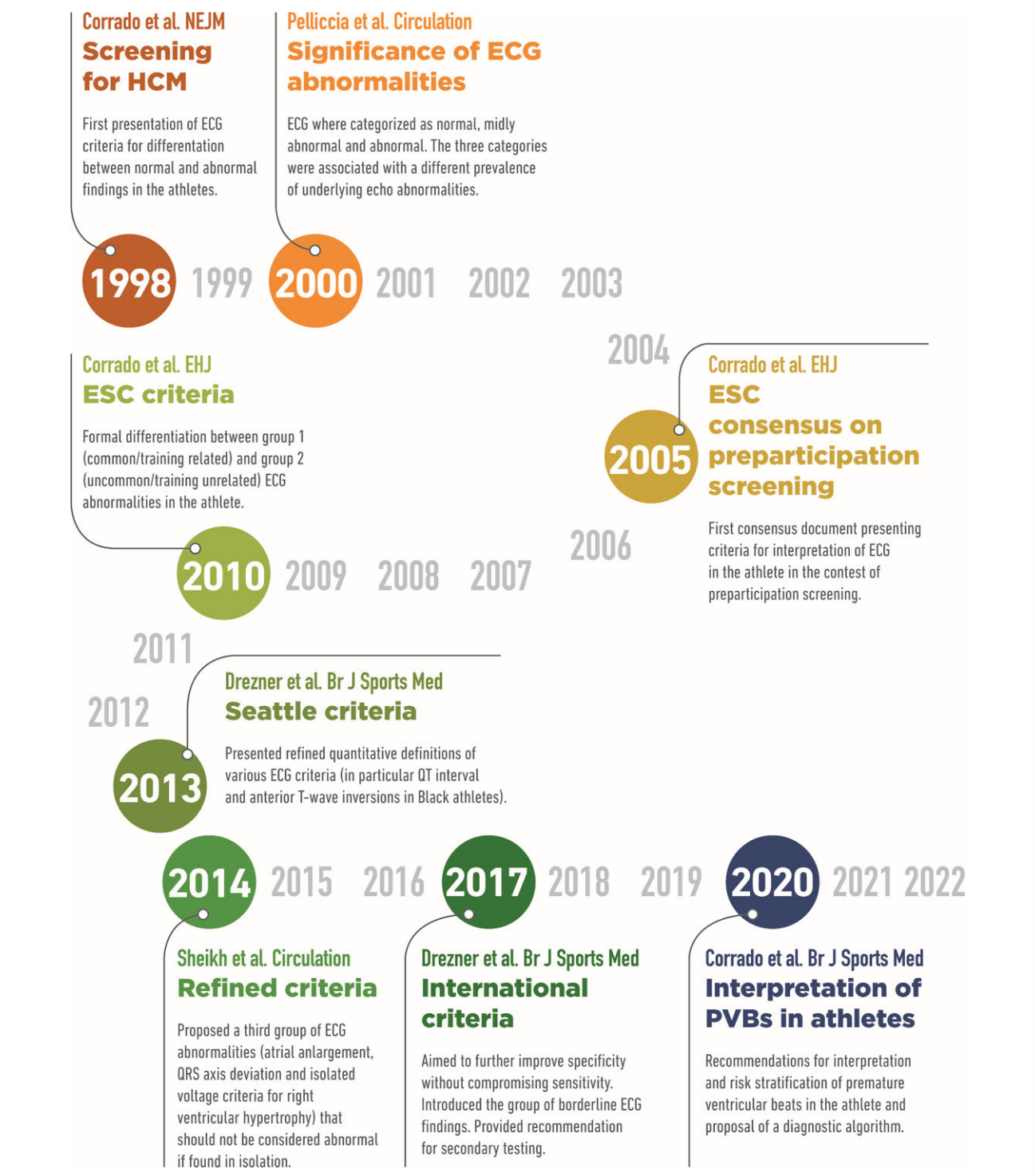

Figure 3 Evolving criteria for interpretation of the athlete's electrocardiogram over the last two decades. In 2010, the original European Society of Cardiology recommendations document introduced the innovative differentiation of physiologic ('common and training-related') electrocardiogram changes from potentially pathologic ('uncommon and training-unrelated') abnormalities, more likely to be reflective of an underlying cardiac disease. This stem document enabled subsequent consensus documents, such as the 2011 Seattle criteria, the 2014 Refined criteria, and the 2017 International criteria, all aimed to provide a more accurate definition of some electrocardiogram parameters and to enhance the diagnostic specificity. In 2020, the interpretation of athlete's electrocardiogram was upgraded with the recommendations for evaluation of ventricular arrhythmias and the proposal of an algorithm for appropriate diagnostic work-up in the athlete.

stratification of athletes with ventricular arrhythmias, particularly based on the morphology of the ectopic QRS complex.[9]

In an article published in the *Lancet* in 2005,[10] we provocatively used a quotation from the Greek dramatist Menander, *those whom the gods love die young* (Ὃν οἱ θεοὶ ϖιλοῦσιν, ἀποθνὴσκει νέος), in reference to SCD among young athletes. We wanted to highlight that, by virtue of the significant insights into our knowledge of the causes, mechanisms, and prevention strategies, and thanks also to the insights by the long-running research programme conducted at the University of Padua, fatalities occurring among young athletes should be no longer considered predestined and beyond our control, but the consequence of an underlying heart disease that may be identified and treated during life.

Conflict of interest: none declared.

References

1. Zampieri F, Zanatta A, Elmaghawry M, Bonati MR, Thiene G. Origin and development of modern medicine at the University of Padua and the role of the "Serenissima" Republic of Venice. *Glob Cardiol Sci Pract* 2013;**2013**:149–162.
2. Thiene G, Nava A, Corrado D, Rossi L, Pennelli N. Right ventricular cardiomyopathy and sudden death in young people. *N Engl J Med* 1988;**318**:129–133.
3. Corrado D, Thiene G, Nava A, Rossi L, Pennelli N. Sudden death in young competitive athletes: clinicopathologic correlations in 22 cases. *Am J Med* 1990;**89**:588–596.
4. Corrado D, Basso C, Schiavon M, Thiene G. Screening for hypertrophic cardiomyopathy in young athletes. *N Engl J Med* 1998;**339**:364–369.
5. Corrado D, Basso C, Pavei A, Michieli P, Schiavon M, Thiene G. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. *JAMA* 2006;**296**:1593–1601.
6. Corrado D, Pelliccia A, Bjørnstad HH, Vanhees L, Biffi A, Borjesson M, *et al.* Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol. *Eur Heart J* 2005;**26**:516–524.
7. Corrado D, Pelliccia A, Heidbuchel H, Sharma S, Link M, Basso C, *et al.* Recommendations for interpretation of 12-lead electrocardiogram in the athlete. *Eur Heart J* 2010;**31**:243–259.
8. Sarto P, Zorzi A, Merlo L, Vessella T, Pegoraro C, Giorgiano F, *et al.* Serial versus single cardiovascular screening of adolescent athletes. *Circulation* 2021;**143**:1729–1731.
9. Corrado D, Drezner JA, D'Ascenzi F, Zorzi A. How to evaluate premature ventricular beats in the athlete: critical review and proposal of a diagnostic algorithm. *Br J Sports Med* 2020;**54**:1142–1148.
10. Corrado D, Basso C, Thiene G. Essay: sudden death in young athletes. *Lancet* 2005;**366**:S47–S48.