International Journal of Cardiology 383 (2023) 166–174

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Electroanatomic mapping in athletes: Why and when. An expert opinion paper from the Italian Society of Sports Cardiology

Antonio Dello Russo [a], Paolo Compagnucci [a], Alessandro Zorzi [b], Elena Cavarretta [c,d], Silvia Castelletti [e], Maurizio Contursi [f], Antonio D'Aleo [g], Flavio D'Ascenzi [h], Lucio Mos [i], Vincenzo Palmieri [j], Giampiero Patrizi [k], Antonio Pelliccia [l], Patrizio Sarto [m], Pietro Delise [n], Paolo Zeppilli [j], Silvio Romano [o], Zefferino Palamà [o,p,*], Luigi Sciarra [o]

[a] Cardiology and Arrhythmology Clinic, University Hospital "Lancisi-Umberto I- Salesi", Ancona, Italy, Department of Biomedical Sciences and Public Health, Marche Polytechnic University, Ancona, Italy
[b] Department of Cardiac, Thoracic and Vascular Sciences and Public Health, University of Padova, Padova, Italy
[c] Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy
[d] Mediterranea Cardiocentro, Naples, Italy
[e] Department of Cardiology, Istituto Auxologico Italiano IRCCS, Milan, Italy
[f] Division of Cardiology, Hospital of Peschiera del Garda, Veneto, Italy
[g] Cardiologia AUSL 7 Distretto di Modica, Ragusa, Italy
[h] Division of Cardiology, Department of Medical Biotechnologies, University of Siena, Siena, Italy
[i] San Antonio Hospital, San Daniele del Friuli, Udine, Italy
[j] Sports Medicine Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[k] Department of Cardiology, Carpi Hospital, Carpi, Italy
[l] Institute of Sport Medicine and Sports Science, Rome, Italy
[m] Sports Medicine Unit, ULSS2, Treviso, Treviso, Italy
[n] Ospedale Pederzoli, Peschiera del Garda, Italy
[o] Department of Life, Health and Environmental Sciences, University of L'Aquila, Aquila, Italy
[p] Casa di Cura Villa Verde, Taranto, Italy

ARTICLE INFO

Keywords:
Cardiomyopathy
Electroanatomical mapping
Ventricular arrhythmias
Sports cardiology

ABSTRACT

Three-dimensional electroanatomical mapping (EAM) has the potential to identify the pathological substrate underlying ventricular arrhythmias (VAs) in different clinical settings by detecting myocardial areas with abnormally low voltages, which reflect the presence of different cardiomyopathic substrates. In athletes, the added value of EAM may be to enhance the efficacy of third-level diagnostic tests and cardiac magnetic resonance (CMR) in detecting concealed arrhythmogenic cardiomyopathies. Additional benefits of EAM in the athlete include the potential impact on disease risk stratification and the consequent implications for eligibility to competitive sports. This opinion paper of the Italian Society of Sports Cardiology aims to guide general sports medicine physicians and cardiologists on the clinical decision when to eventually perform an EAM study in the athlete, highlighting strengths and weaknesses for each cardiovascular disease at risk of sudden cardiac death during sport. The importance of early (preclinical) diagnosis to prevent the negative effects of exercise on phenotypic expression, disease progression, and worsening of the arrhythmogenic substrate is also addressed.

1. Introduction

Italian pre-participation screening in competitive sports has represented an important form of protection for athletes since the early 1980s. In Italy, the sports doctor certifies the eligibility to competitive sports under his or her responsibility. The European guidelines [1] and, more restrictively, the Italian ones [2] represent a guide in defining the criteria for eligibility and disqualification to sports practice for subjects with cardiovascular (CV) abnormalities.

Physical exercise is associated with several beneficial effects on

* Corresponding author at: Department of Life, Health and Environmental Sciences, University of L'Aquila, Aquila, Italy.
E-mail address: zefferino.palama@icloud.com (Z. Palamà).

https://doi.org/10.1016/j.ijcard.2023.05.013
Received 18 February 2023; Received in revised form 21 April 2023; Accepted 10 May 2023
Available online 11 May 2023

health. Nevertheless, it can trigger life-threatening arrhythmias and sudden cardiac death (SCD) in those athletes affected by an underlying arrhythmogenic cardiomyopathy (CMP) [3,4].

Arrhythmogenic CMPs are a heterogeneous disease group of the myocardium characterized by structural, mechanical, and electrical abnormalities. These conditions refer to a wide group of etiologies and associated genetic, infectious, metabolic, or neuromuscular conditions.

Athletes may remain asymptomatic for a long time or, with the progression of the disease, develop symptoms related to heart failure or arrhythmias, syncope or cardiac arrest. The latter may be the disease's first and most dramatic clinical manifestation. A multiparametric approach with the integration of imaging and clinical data, familiar history and genetic analysis [5], is crucial for the complete assessment of suspected cardiac life-threatening conditions, such as inherited heart diseases (IHD). Unfortunately, in daily clinical practice, the classification and stratification of subjects with ventricular arrhythmias and suspected CMP or inherited cardiac disorder remain very complex. Diagnostic and prognostic evaluation of these athletes with possible CMP includes resting ECG [6], ambulatory ECG monitoring [7], ECG stress testing [8], echocardiographm [9] and advanced imaging such as cardiac magnetic resonance (CMR) and cardiac computed tomography CT [10,11] and however, sometimes grey areas remain.

Electroanatomical mapping may play a role in resolving doubtful cases [12]. The present document of the Italian Society of Sports Cardiology aims to assist general sports medicine physicians and sports cardiologists with the clinical decision as to why and when to perform an electroanatomical mapping on the athlete.

2. Ventricular arrhythmias in athletes

Ventricular arrhythmias (VAs) in athletes without evidence of structural heart disease after noninvasive evaluation has been associated with a good prognosis and do not represent a reason for disqualification from competitive sports [13]. However, many areas of uncertainty remain in the exclusion of possible CMPs.

In daily clinical practice, the simple ECG can guide the sports medicine doctor in the diagnostic and prognostic setting. The presence of abnormal ECG patterns [14] or particular VAs features increases the suspicion of underlying IHDs. Premature ventricular contraction characteristics, such as complexity and morphology, are essential criteria for guiding the final diagnosis and estimating the risk in competitive athletes. Recent studies have suggested that the morphology of VAs, rather than the frequency, may be the key feature to identify possible underlying CMPs [15,16]. Idiopathic VAs are characterized by the absence of underlying structural heart disease and a favorable prognosis and exhibit distinctive ECG patterns (infundibular and fascicular) [17]. On the other hand, uncommon patterns require a careful and extensive screening program to exclude concealed CMPs. After first-line examination (ambulatory ECG monitoring [18], stress testing [19], echocardiography), athletes with a ‘common’ PVB pattern do not require further testing and can be considered eligible for competitive sports, unless other suspicious findings (e.g. family history for sudden cardiac death, unexplained syncope, ECG abnormalities suggesting possible cardiomyopathy…) are present. On the contrary, athletes with an ‘uncommon’ PVB pattern should undergo a contrast-enhanced MRI, regardless of symptoms or familial background or the results of first-line examinations, to rule out a concealed myocardial substrate at risk of malignant arrhythmic events during sports activity. Genetic testing particularly for the exclusion of cathecolaminergic ventricular tachycardia may be also needed in selected cases [5].

3. The electrophysiological study in sports cardiology

The electrophysiological study (EPS) also represents an important means of invasive diagnostics in sports cardiology. For example, the EPS role is decisive in diagnosing and treating supraventricular tachycardias and classifying paroxysmal atrial fibrillation triggers in athletes [2–20]. In the context of the prevention of SCD, the role of EPS is still controversial. Indeed, while for of prognostic stratification of type 1 Brugada [21], EPS could have a role inserted in a multiparameter workflow, it is more debated in drug-induced type 1 pattern [22]. The role of EPS in the context of CMPs/IHDs is even more debated. EPS alone might play a role in patients with arrhythmogenic CMP (ACM) or dilated CMP (DCM), while it does not contribute to identifying high-risk patients affected by hypertrophic CMP (HCM) [23–25].

4. Electroanatomical mapping in sports cardiology: Literature review

Electroanatomical mapping (EAM) with endocardial catheters has now entered its third decade in the clinical arena [26–28]. Initially and primarily introduced as a technique to facilitate catheter ablation by allowing activation mapping of cardiac arrhythmias [27,28] and facilitating movements of catheters towards ablation targets without fluoroscopic guidance, the value of EAM is rapidly growing. Three-dimensional EAM has been demonstrated to potentially identify the pathological substrate underlying VAs in different clinical settings by detecting electroanatomical scar, i.e. myocardial areas with abnormally low electrogram voltages with evidence of fragmented signals, which reflect the presence of different cardiomyopathic substrates [29,30]. This method could be therefore integrated within the workflow of the SCD stratification in subjects with concealed CMPs through an in-depth tissue characterization (Fig. 1).

In 2005, Corrado et al. demonstrated the diagnostic value of EAM among patients fulfilling noninvasive 1994 Task Force criteria for ACM. In the study, of 31 young (mean age, 31 ± 7 years) patients undergoing right ventricular endocardial EAM, 20 patients had low-voltage and fractionated electrogram regions, where fibrofatty replacement could be histologically demonstrated in 75% of cases; on the other hand, the remaining 11 did not have evidence of low voltage-prolonged duration electrograms, and active myocarditis could be diagnosed by endomyocardial biopsy 91% of times. In this work, the prognostic value of EAM clearly emerged in those patients with abnormal EAM who showed a significantly higher risk of sustained ventricular tachycardia/unexplained syncope during follow-up than those with normal EAM [31]. A more recent work from the same group confirmed that EAM is closely correlated to histopathological findings in ARVC patients, the endocardial electroanatomical scar indicating the presence of fibrofatty replacement of the myocardium; furthermore, the extension of right ventricular endocardial low-voltage electrogram area was a strong independent predictor of major arrhythmic events during follow-up [32].

An important contribution to the understanding of EAM's role in sports cardiology came in 2011 when Dello Russo and colleagues reported data on 13 competitive athletes with complex VAs (sustained ventricular tachycardia, $n = 3$; frequent nonsustained ventricular tachycardia, $n = 7$; >1000 premature ventricular complexes/24 h, $n = 3$) and apparently structurally normal hearts after noninvasive evaluation (including signal-averaged ECG, echocardiography, and cardiac magnetic resonance imaging). Remarkably, 12/13 patients (92%) had one or more low-voltage regions at endocardial EAM, and a diagnosis of myocarditis ($n = 7$) or arrhythmogenic right ventricular cardiomyopathy ($n = 5$) could be formulated by EAM-guided endomyocardial biopsy, underlining the relevance of EAM findings and their implications for the assessment of sports eligibility [12].

On the same line, Narducci et al. conducted a study enrolling competitive athletes ($n = 18$) and nonathletes ($n = 15$) with complex VAs of mainly right ventricular outflow tract origin and without structural heart disease at echocardiography. CMR showed late gadolinium enhancement in 9 subjects (athletes, $n = 5$). All patients underwent endocardial EAM, which disclosed electroanatomical scar zones in the right ventricle in 14 subjects (athletes, $n = 8$), and in the left ventricle in 6 subjects (athletes, $n = 3$); the electroanatomical scar's most common

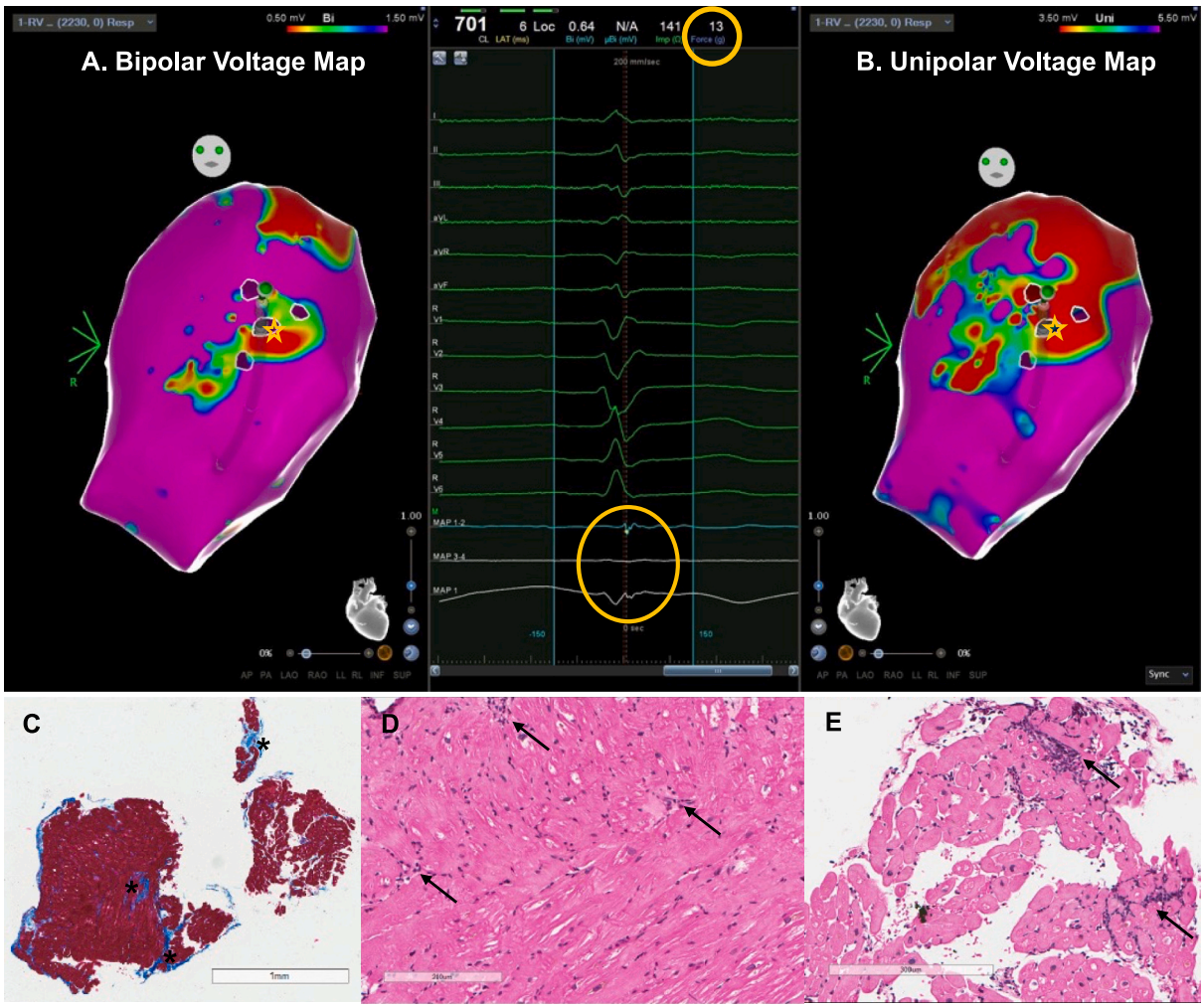

Fig. 1. Point-by-point contact force-guided electroanatomical voltage map in a 29-year-old cyclist with left bundle branch block inferior axis premature ventricular complexes, non-dilated left ventricle with preserved ejection fraction, and left ventricular anterior-lateral nonischemic scar at gadolinium-enhanced cardiac magnetic resonance, with negative results of genetic testing (dilated and arrhythmogenic cardiomyopathy panels). A: the bipolar voltage map shows a limited low-voltage area in the basal and mid segments of the left ventricular anterior-lateral wall. B: the unipolar voltage map shows a larger corresponding low-voltage region, consistent with a prevalently epicardial scar. In the target area, four electroanatomical mapping-guided endomyocardial biopsies (C-E) are performed [holes and yellow star]; note that both bipolar and unipolar electrograms in the target area have low amplitude and fractionation (lower yellow circle), despite the good catheter-tissue contact (13 g, upper yellow circle) (purple: healthy tissue; yellow, green and blue: intermediate voltages involved in border scar zone; red: dense scar areas; for bipolar and unipolar voltage cutoffs see 5.2.1 chapter). C: endomyocardial biopsy sample showing multifocal replacement-type fibrosis (asterisks; trichrome stain); D-E, close-ups showing inflammatory cells (arrows) near areas of fibrosis and patchy necrosis (hematoxylin and eosin stain). Polymerase chain reaction studies excluded the presence of viral genomes, consistent with a final diagnosis of chronic active virus-negative lymphocytic myocarditis, which prompted disqualification from sports. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

location was the right ventricular outflow tract. Interestingly, the authors found low concordance for the detection of scars between cardiac magnetic resonance imaging and EAM (Cohen kappa = −0.09). All athletes were advised to stop training, and during a median follow-up of 18.7 months, the risk of VA persistence was significantly lower in detrained athletes than in non-athletes [33,34].

Although the literature specifically concerning the use of EAM in athletes with ventricular arrhythmias is limited to the studies mentioned above and to others discussed in Section 6, other investigations conducted in nonathletes offer important insights on the role of EAM as a clinical tool to characterize the myocardial substrate underlying complex VAs.

Several recent reports have shown that late gadolinium enhancement-CMR sequences may be more sensitive than EAM with conventional voltage cutoffs for identifying scars in the left ventricle, especially in thick myocardial wall regions and in the presence of non-transmural scars [33–35]. However, in the thinner-walled right ventricle, late gadolinium enhancement may be less accurate, and in fact, several reports concerning patients with VAs of right ventricular origin [36], as well as patients with ACM, support the concept that endocardial EAM may be preferable for the detection of small RV scar areas.

Therefore, according to the authors, endocardial EAM might be an additional tool in the diagnostic approach to the athlete presenting with complex and uncommon ventricular arrhythmias [15,16] of presumed right ventricular origin, both as an isolated tool and as a preliminary step for EAM-guided endomyocardial biopsy, especially in cases with negative or doubtful CMR and strong clinical suspicion of CMPs (i.e family history, syncope, surface ECG alterations, etc). When VAs have a presumed left ventricular origin, EAM has a key role in the case of indications for VA ablation. Due to its invasive nature and the higher risk profile compared to endocardial EAM (approximately 5% risk of major complications among patients undergoing epicardial VA ablation), epicardial EAM should only be performed in case of indications for

epicardial ablation for VAs [37].

5. How to perform electroanatomical mapping

5.1. Technological basis of electroanatomical mapping

The basic principles underlying EAM are as follows:

1) the possibility of visualizing the position of the mapping/ablation catheter in real-time on a computer screen, with no need to use fluoroscopy;
2) the capability to reconstruct the detailed three-dimensional surface of a given cardiac chamber while at the same time tagging this surface with local electrical information, including bipolar voltage amplitude, unipolar voltage amplitude, the presence of fractionated or late electrograms, or activation timing, which are visually displayed by means of color-coded three-dimensional maps.

The main available electroanatomical mapping systems mainly differ in the technology used for three-dimensional catheter location in the mapping space, i.e. magnetic-based, impedance-based, or a combination of the two.

The CARTO mapping system (Biosense Webster, USA), which was first introduced in clinical practice in the late 1990s [26,27], uses the ultralow-intensity magnetic field produced by a location pad underneath the operating table. The catheter's tip carries magnetic sensors, which measure the magnetic field's strength and allow calculating the distance between the catheter's tip and the pad. Furthermore, the magnetic field's strength measured by the catheter's tip is compared with that measured by reference pads on the patient's chest and back to compensate for slight patient movements [26–28].

On the other hand, the EnSite NavX system (Abbott Medical, USA) uses impedance to locate the catheter's tip. An alternating current flows between three orthogonal pairs of surface electrodes on the patient's back and the location of the catheter is derived according to the intensity of the current recorded by the catheter's electrodes [38,39]. The more recent versions of the system, EnSite Precision and EnSiteX, allow greater precision in the catheter's location by incorporating magnetic field technology, thus correcting for the inhomogeneous distribution of impedance inside the patient's chest and impedance changes caused by saline irrigation of the catheter's tip [38,39].

The third most widely available mapping system is Rhythmia (Boston Scientific, USA), which uses a combination of magnetic and impedance-based technology to optimize the system's accuracy in the catheter's location [40].

5.2. Electrogram analysis

From a sports cardiology perspective, electroanatomical voltage mapping and late/fragmented potentials annotation are the most useful techniques allowing the identification and accurate characterization of the arrhythmogenic myocardial substrate [41]. These techniques rely on the characterization of some features of recorded electrograms, i.e. amplitude, duration, and fragmentation, which were validated in histopathologic and imaging studies as markers of disease processes associated with the risk of life-threatening ventricular arrhythmias. The electroanatomical scar is diagnosed in the presence of low voltage electrograms with evidence of fragmented signals, and it represents the hallmark of a potentially arrhythmogenic myocardial substrate.

5.2.1. Electrogram amplitude

Electrogram peak-to-peak maximum voltage is a key marker of replacement fibrosis and/or fibrous-fatty infiltration. In fact, in these pathologic processes, the myocardium is replaced by electrically inert fibrous or fatty tissue, leading to lower-amplitude electrograms. The amplitude of recorded electrograms, however, depends on several technical issues, including but not limited to the size of mapping electrodes, interelectrode spacing, the orientation of the mapping catheter with respect to wavefront propagation, and the adequacy of catheter-tissue contact [42,43].

Using 3.5–4.0 mm-tip electrode catheters with 1 mm-ring electrode, 2 mm interelectrode spacing and 10–400 Hz filtering, conventional endocardial bipolar voltage cutoffs for the identification of healthy myocardium and dense scar are $\geq$1.5 mV and $<$ 0.5 mV, respectively, with areas displaying bipolar peak-to-peak voltage between 0.5 and 1.5 mV labeled as border zone regions (Fig. 1) [44]; these cutoffs were validated against histological and imaging data, and are used for both left ventricular and right ventricular mapping [43]. Noteworthy, being the bipolar electrogram recorded between the distal tip and the proximal ring electrodes, the peak-to-peak bipolar electrogram amplitude is exquisitely sensitive to disease processes involving the endocardium and subendocardium, as in the case of ischemic cardiomyopathy [45].

On the other hand, unipolar electrograms are recorded between the tip electrode and Wilson central terminal; therefore, unipolar electrograms have a wider field of view, and endocardial unipolar peak-to-peak electrogram amplitude is thus reflective of epicardial and/or mid-myocardial disease processes, typically encountered in nonischemic cardiomyopathies, and which may be underappreciated by only relying on endocardial bipolar electrogram amplitude (Fig. 1) [46,47]. Proposed peak-to-peak endocardial unipolar voltage cutoff values for the detection of low-voltage epicardial areas are $<$5.5 mV in the right ventricle [46] and $<$ 8.3 mV in the left ventricle, although some cardiac magnetic resonance- or whole heart histology-based studies have shown that there may be overlap in endocardial unipolar electrogram amplitude in regions with and without an intramural-epicardial scar [48].

5.2.2. Late/fragmented potentials annotation

Besides electrogram amplitude, late potentials are key signs of an arrhythmogenic substrate. In fact, in disease processes characterized by fibrous or fibro/fatty replacement of the myocardium (myocardial infarction, cardiomyopathies, myocarditis), surviving myocytes may be inhomogeneously interspersed among bundles of connective tissue, producing slow and three-dimensionally complex patterns of propagation of the electrical impulse, which have been referred to as “zigzag” course of activation [49]. At the electrogram level, these electrophysiological phenomena are associated with the presence of late and fractionated electrograms, which may be recorded in scarred myocardial regions, and highlight the arrhythmogenicity of the myocardial substrate; in this regard, late potentials are considered more specific markers of a possible ventricular tachycardia circuit, while fragmented potentials may be recorded in more widespread scar regions [50,51]. The possibility of recording late potentials may be hampered in the presence of large far-field electrograms obscuring abnormal local activity. Under these circumstances, pacing maneuvers with extra stimuli may help reveal abnormal local conduction and late potentials, unmasking the arrhythmogenicity of the myocardial substrate [52].

5.3. Standardized diagnostic interpretation of electroanatomical mapping in sports cardiology

In order to render EAM findings reliable and less subject to interpretation, these authors propose the following criteria for the definition of abnormal EAM findings:

1) an adequate catheter-tissue contact should be confirmed by preferring contact-force sensing catheters (see following discussion) and ensuring a contact force $\geq$5 g for point acquisition;
2) electrogram abnormalities (low-voltage electrograms [$<$1.5 mV in bipolar maps, $<$5.5 mV in unipolar right ventricular maps, $<$8.3 mV in unipolar left ventricular maps] and/or late [i.e., extending beyond the end of the surface QRS complex]/fragmented [3 or more sharp

components] electrograms) should cover a minimum of 4 cm^2 of the endocardial surface, using a maximum fill threshold of 10.

Regarding the first point, although published data suggest that multipolar mapping catheters with small electrodes and short inter-electrode distance may help unveil late potentials [43,53], the authors believe that the use of contact force sensing ablation catheters may help avoid erroneous detection of low-voltage regions due to inadequate catheter-tissue contact, and therefore contact-force sensing ablation catheters should be preferred. During mapping, care should be taken to ensure a contact force of at least 5 g at each acquired point. In future years, novel contact force-sensing ablation catheters equipped with microelectrodes may combine the advantages of high-resolution mapping with contact force-sensing capability, potentially becoming the gold standard for substrate assessment [54–56]. However, we currently lack large-scale data on this technology's use in human subjects [56].

Regarding the second point, the authors recognize that the diagnostic/prognostic role of very small areas of electrogram abnormalities is currently uncertain. Importantly, in case an inadequate number of mapping points is taken, and the fill threshold is therefore increased over 10, mapped points may be interpolated over a large area, with consequent distortion of the mapped anatomy and inaccurate reflection of the myocardial substrate in voltage maps [42]. Therefore, we suggest that at least 200 points be acquired in each mapped ventricular chamber for diagnostic EAM in athletes.

5.4. Proposed integration of electroanatomical mapping and clinical data for prognostic assessment

The presence of scar associated with late potentials should be considered an important marker of an increased risk of ventricular tachycardia in the context of concealed IHDs.

In the presence of an isolated scar (without late potentials), the full patient presentation should be assessed, and both endomyocardial biopsy (see later section) and genetic testing may be of help [41,57].

The presence of a large scar (>10% of the mapping surface), ventricular tachycardia inducibility, histological criteria for arrhythmogenic cardiomyopathy or myocarditis, or detection of pathogenic/probably pathogenic variants of genes associated with cardiomyopathies represent markers of risk and should be carefully considered in assessing eligibility to competitive sports activity.

6. The role of endomyocardial biopsy in Sports Cardiology

The ultimate decision on sports eligibility of athletes presenting with complex and uncommon VAs depends on the underlying myocardial substrate. As such, it is pivotal to reach a definite diagnosis using all available diagnostic tools, from imaging with echocardiography and CMR to genetic testing when appropriate [1,2].

In case the imaging picture does not allow drawing definite conclusions on the presence or absence of significant structural heart disease, and also in the presence of genetic variants of unknown significance, an EAM-guided endomyocardial biopsy may help reach a definite diagnosis, different from that clinically suspected [41,58–62].

In a seminal 2020 paper, Casella et al. demonstrated that among non-athlete patients (mean age, 41 ± 15) mainly presenting with VAs, EAM-guided endomyocardial biopsy, which involved endomyocardial sampling directly from areas showing low bipolar/unipolar voltages, allowed to reach a different diagnosis from what was suspected based on clinical/imaging data in more than one-third of the study population (39%) [60]. EAM had similar sensitivity to CMR imaging for the detection of underlying CMP, while also having nonsignificantly higher specificity [60]. Interestingly, in 12 patients with EMB-proven cardiomyopathy, EAM identified pathological areas that could not be identified by CMR [60]. Of note, the population included in the study had very high prevalence of myocardial fibrosis, as testified by the 71% prevalence of late gadolinium enhancement, thus supporting the use of EAM and endomyocardial biopsy among patients with VAs and myocardial scar [60].

On the same line, Dello Russo et al. recently reported on the role of an extensive diagnostic workup, including EAM and EAM-guided endomyocardial biopsy, among athletes presenting with complex ventricular arrhythmias. Of note, 42 athletes underwent endomyocardial biopsy, with a 50% (n = 21) diagnostic reclassification rate and few procedural complications mainly linked to vascular access [41].

Therefore, according to the authors, an endocardial EAM-guided endomyocardial biopsy may be considered as additional diagnostic tool among athletes presenting with complex VAs and unclear findings after comprehensive clinical-imaging assessments and genetic testing. The evidence supporting right ventricular sampling is currently stronger than those supporting biventricular or left ventricular sampling [63], and in fact right ventricular EAM-guided endomyocardial biopsy may be considered for the etiological evaluation of patients presenting with a first sustained monomorphic ventricular tachycardia episode according to the most recent European Society of Cardiology (ESC) guidelines on the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death [64]. Left ventricular EAM and EAM-guided endomyocardial biopsy may be considered in case of unclear cardiac magnetic resonance findings limited to the left ventricle, but this procedure is more complex, and should be performed in selected cases, by experienced operators in high-volume centers. Endomyocardial biopsy examination can also be repeated at a distance, in order to reconstruct the anatomopathological mechanism underlying the fibrotic process, differentiating primitive arrhythmogenic forms from myocardial forms (e.g. lymphocytic myocarditis, with consequent therapeutic implications) [41,60–65]. The potential risks of the invasive procedure should be weighed against the advantages in terms of diagnostic reclassification, and the athlete should be involved in a shared decision-making process, especially in the case of left ventricular endomyocardial biopsy, for which international guidelines are currently lacking clear indications for the assessment of patients with VAs [64].

7. Electroanatomic mapping in daily clinical practice: Limitations

The EAM may represent a potentially decisive diagnostic tool in some doubtful cases, however, like any diagnostic tool in sports cardiology, it has no value if not inserted within clinical and deductive reasoning. Furthermore, several limitations are inherent in the technique, including its elevated costs, its operator dependency, and the potential risk of inadequate/inaccurate interpretation of EAM results. These considerations relegated EAM-guided endomyocardial biopsy as a third/fourth level assessment in 2022 ESC guidelines, to be considered in patients presenting with a first sustained monomorphic ventricular tachycardia, after CMR and in order to obtain a tissue diagnosis of ARVC or inflammatory cardiomyopathies (class of recommendation IIb, level of evidence C) [64].

The indication for the execution of an endocardial EAM (with or without biopsy) in athletes should therefore be placed only after the execution of a “Sport Hearth Team” including a sports doctor, a clinical cardiologist, an imaging cardiologist and an arrhythmologist (with adequate experience in this technique and in sports cardiology). In fact, if on the one hand, the endocardial EAM can provide valuable information to complete non-invasive tests (i.e. suspicious CMR for arrhythmogenic cardiomyopathy which is confirmed with the EAM in the characterization of the right ventricular outflow tract), on the other hand, it can provide isolated information that is difficult to insert within the clinical context (i.e. isolated subepicardial right ventricular outflow tract scar) [66].

Therefore, EAM should be reserved for selected athletes with uncommon (atypical right bundle branch block and QRS duration ≥130 ms, left bundle branch block and superior/intermediate axis,

polymorphic VAs) and/or complex arrhythmia patterns (short coupling PVBs, exercise-induced VAs, nonsustained/sustained ventricular tachycardia), and when CMR raises doubts or is inconclusive, i.e. in case of strong suspicion of CMPs/IHDs [12,67]. By contrast, EAM should not be used in cases of common arrhythmias in athletes with negative family history and non-invasive diagnostic tests (i.e. typically, infundibular or fascicular arrhythmias with an indication of ablation for palpitations) [67]. Being epicardial EAM a more invasive test and given that some electrophysiological characteristics of the epicardium may be assessed with endocardial unipolar EAM, these authors do not recommend epicardial EAM solely for diagnostic purposes. Epicardial EAM should be performed when there is an indication for epicardial ablation of VAs [37].

As a corollary, phase-specific considerations apply to athletes with clinically-suspected myocarditis [65,68]. In fact, in the acute myocarditis phase, myocardial inflammation may render the myocardial substrate more electrically unstable and vulnerable, therefore facilitating sustained VA inducibility by EPS, and making EPS less specific for the long-term prediction of major arrhythmic events [69]. Furthermore, endocardial EAM may be completely normal in acute myocarditis with scarce/absent myocardial fibrosis, potentially offsetting the clinical utility of EAM in this setting [65]. By contrast, EPS and EAM may help to better characterize the arrhythmogenicity of the myocardial substrate of patients with clinically-suspected non-acute myocarditis (i.e., when CMR reveals myocardial fibrosis and/or several weeks have passed since the onset of symptoms; non-acute myocarditis includes chronic active and healed myocarditis [post-inflammatory myocardial scar]), by revealing the extension of low-voltage regions and the presence of late potentials [65,68,69]. Of note, endomyocardial biopsy (with or without EAM guidance) is required for the definite diagnosis of myocarditis in each phase of the disease, may provide prognostic information, and may inform patient-tailored etiology-driven therapies (i.e. allowing the prescription of immunosuppressive therapy in case of endomyocardial biopsy-proven virus-negative myocarditis and in giant cell myocarditis) [62,65,71,72], and these recommendations may also apply to athletes [68].

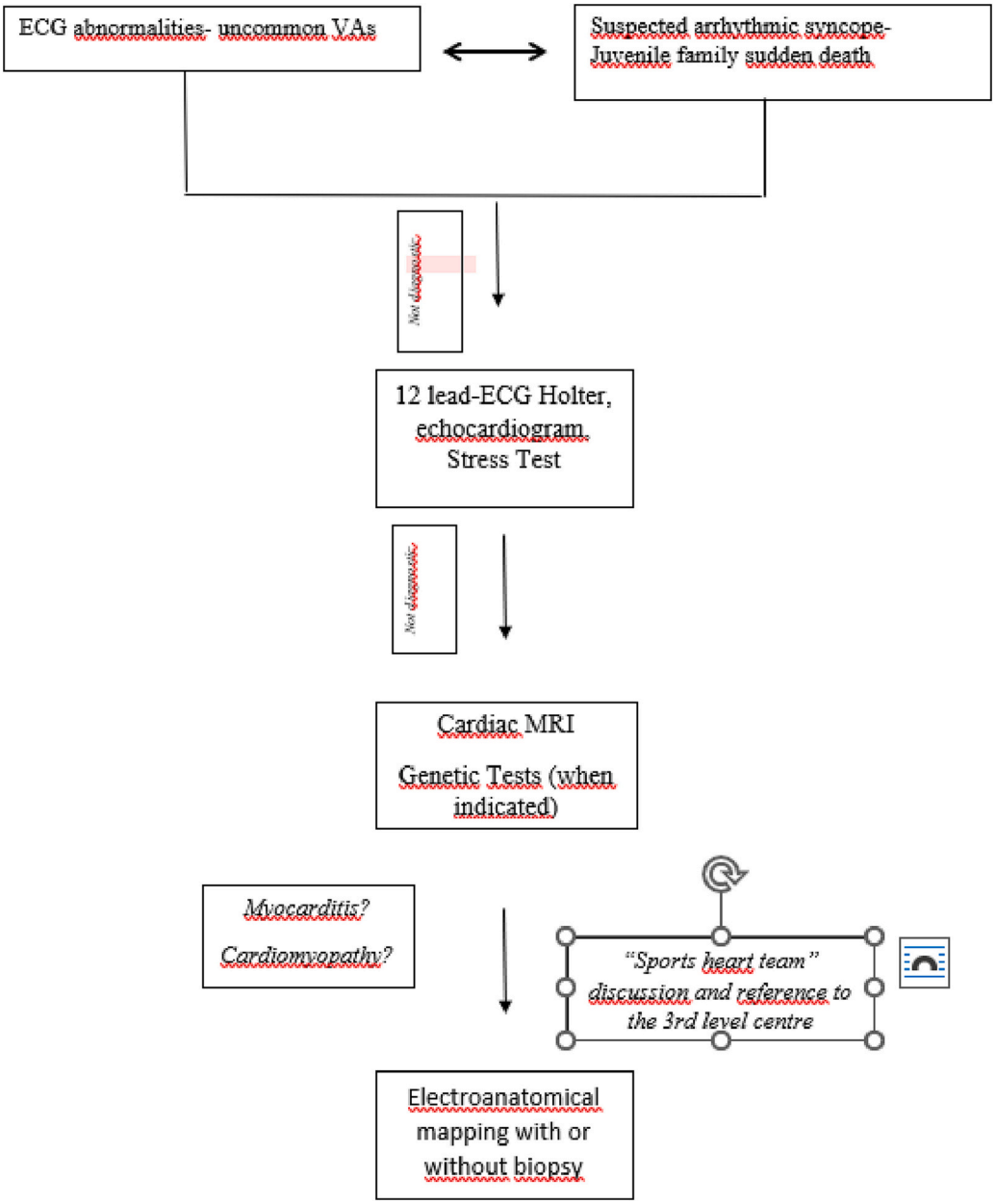

Fig. 2. Workflow including when EAM can be useful to untangle the skein of suspected inherited heart disease.

8. When to perform an electroanatomic mapping in athletes: Summarizing

The classification and stratification of subjects with VAs and suspected arrhythmogenic cardiomyopathy remain complex.

A workflow including when EAM can be useful to untangle the skein is summarized in Fig. 2. The role of electroanatomical mapping is particularly relevant in the differentiation between myocarditis and forms of ACM, especially if integrated with the biopsy and histological examination that allows sampling in an extremely precise way of the areas of altered voltage, and expression of myocardial fibrosis [41–60,68].

A careful analysis of the patient's clinical and family history (suspected arrhythmic syncope and history of juvenile family sudden death) combined with the ECG abnormalities [70] or the presence of VAs (especially if with non-common morphology [67]) must require that the consulting physician continue the diagnostic workflow. When ambulatory ECG monitoring, stress test and echocardiography are not conclusive, especially in the forms of concealed cardiomyopathies, genetic tests, CMR and endocardial EAM with possible endomyocardial biopsy represent third-level tests to be integrated into the diagnostics workflow, also considering the above limitations. Therefore, a case-by-case discussion in a "Sport Hearth Team" appears to be reasonable both to indicate the EAM execution and the interpretation of the collected data within a comprehensive workup.

References

[1] A. Pelliccia, S. Sharma, S. Gati, M. Bäck, M. Börjesson, S. Caselli, J.P. Collet, D. Corrado, J.A. Drezner, M. Halle, D. Hansen, H. Heidbuchel, J. Myers, J. Niebauer, M. Papadakis, M.F. Piepoli, E. Prescott, J.W. Roos-Hesselink, A. G. Stuart, R.S. Taylor, P.D. Thompson, M. Tiberi, L. Vanhees, M. Wilhelm, 2020 ESC guidelines on sports cardiology and exercise in patients with cardiovascular disease, Rev. Esp. Cardiol. (Engl. Ed.) 74 (6) (2021 Jun) 545. English, Spanish, https://doi.org/10.1016/j.rec.2021.05.003. PMID: 34020769.

[2] P. Delise, L. Mos, L. Sciarra, C. Basso, A. Biffi, F. Cecchi, F. Colivicchi, D. Corrado, A. D'Andrea, E. Di Cesare, A. Di Lenarda, S. Gervasi, F. Giada, V. Guiducci, G. Inama, L. Leoni, Z. Palamà, G. Patrizi, A. Pelliccia, M. Penco, A.G. Robles, S. Romano, F. Romeo, P. Sarto, B. Sarubbi, G. Sinagra, P. Zeppilli, Italian Cardiological guidelines (COCIS) for competitive sport eligibility in athletes with heart disease: update 2020, J. Cardiovasc. Med. (Hagerstown) 22 (11) (2021 Dec 1) 874–891, https://doi.org/10.2459/JCM.0000000000001186.

[3] B.J. Maron, W.C. Roberts, H.A. McAllister, D.R. Rosing, S.E. Epstein, Sudden death in young athletes, Circulation 62 (1980) 218–229, https://doi.org/10.1161/01.cir.62.2.218.

[4] D. Corrado, C. Basso, G. Rizzoli, M. Schiavon, G. Thiene, Does sports activity enhance the risk of sudden death in adolescents and young adults? J. Am. Coll. Cardiol. 42 (2003) 1959–1963, https://doi.org/10.1016/j.jacc.2003.03.002.

[5] S. Castelletti, A. Zorzi, E. Ballardini, C. Basso, A. Biffi, F. Brancati, E. Cavarretta, L. Crotti, M. Contursi, A. D'Aleo, F. D'Ascenzi, P. Delise, A. Dello Russo, G. Gazale, L. Mos, V. Novelli, Z. Palamà, S. Palermi, V. Palmieri, G. Patrizi, A. Pelliccia, K. Pilichou, S. Romano, P. Sarto, P.J. Schwartz, M. Tiberi, P. Zeppilli, D. Corrado, L. Sciarra, Molecular genetic testing in athletes: why and when a position statement from the Italian Society of Sports Cardiology, Int. J. Cardiol. (2022 Jun 1), https://doi.org/10.1016/j.ijcard.2022.05.071. S0167-5273(22)00818-X.

[6] J. Luebbert, D. Auberson, F. Marchlinski, Premature ventricular complexes in apparently Normal hearts, Card Electrophysiol. Clin. 8 (3) (2016 Sep) 503–514, https://doi.org/10.1016/j.ccep.2016.04.001.

[7] P. Hingorani, D.R. Karnad, P. Rohekar, V. Kerkar, Y.Y. Lokhandwala, S. Kothari, Arrhythmias seen in baseline 24-hour Holter ECG recordings in healthy Normal volunteers during phase 1 clinical trials, J. Clin. Pharmacol. 56 (7) (2016 Jul) 885–893, https://doi.org/10.1002/jcph.679.

[8] A. Zorzi, T. Vessella, M. De Lazzari, A. Cipriani, V. Menegon, G. Sarto, R. Spagnol, L. Merlo, C. Pegoraro, M.P. Marra, D. Corrado, P. Sarto, Screening young athletes for diseases at risk of sudden cardiac death: role of stress testing for ventricular arrhythmias, Eur. J. Prev. Cardiol. 27 (3) (2020 Feb) 311–320, https://doi.org/10.1177/2047487319890973.

[9] G. Pontone, A.I. Guaricci, D. Andreini, A. Solbiati, M. Guglielmo, S. Mushtaq, A. Baggiano, V. Beltrama, L. Fusini, C. Rota, C. Segurini, E. Conte, P. Gripari, A. Dello Russo, M. Moltrasio, F. Tundo, F. Lombardi, G. Muscogiuri, V. Lorenzoni, C. Tondo, P. Agostoni, A.L. Bartorelli, M. Pepi, Prognostic benefit of cardiac magnetic resonance over transthoracic echocardiography for the assessment of ischemic and nonischemic dilated cardiomyopathy patients referred for the evaluation of primary prevention implantable cardioverter-defibrillator therapy, Circ. Cardiovasc. Imaging 9 (10) (2016 Oct), e004956, https://doi.org/10.1161/CIRCIMAGING.115.004956.

[10] R.G. Assomull, S.K. Prasad, J. Lyne, G. Smith, E.D. Burman, M. Khan, M. N. Sheppard, P.A. Poole-Wilson, D.J. Pennell, Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy, J. Am. Coll. Cardiol. 48 (10) (2006 Nov 21) 1977–1985, https://doi.org/10.1016/j.jacc.2006.07.049.

[11] F. D'Ascenzi, A. Baggiano, L. Cavigli, G.E. Mandoli, D. Andreini, C. Marallo, S. Valente, M. Focardi, M. Cameli, G. Pontone, The role of cardiac computed tomography in sports cardiology: back to the future!, Eur. Heart J. Cardiovasc. Imaging 23 (11) (2022 Oct 20) e481–e493, https://doi.org/10.1093/ehjci/jeac069 (PMID: 35434740).

[12] A. Dello Russo, M. Pieroni, P. Santangeli, S. Bartoletti, M. Casella, G. Pelargonio, C. Smaldone, M. Bianco, L. Di Biase, F. Bellocci, P. Zeppilli, C. Fiorentini, A. Natale, C. Tondo, Concealed cardiomyopathies in competitive athletes with ventricular arrhythmias and an apparently normal heart: role of cardiac electroanatomical mapping and biopsy, Heart Rhythm. 8 (12) (2011 Dec) 1915–1922, https://doi.org/10.1016/j.hrthm.2011.07.021.

[13] A. Biffi, A. Pelliccia, L. Verdile, F. Fernando, A. Spataro, S. Caselli, M. Santini, B. J. Maron, Long-term clinical significance of frequent and complex ventricular tachyarrhythmias in trained athletes, J. Am. Coll. Cardiol. 40 (3) (2002 Aug 7) 446–452, https://doi.org/10.1016/s0735-1097(02)01977-0.

[14] H.K. Terho, J.T. Tikkanen, T.V. Kenttä, J.M. Junttila, A.L. Aro, O. Anttonen, T. Kerola, H.A. Rissanen, P. Knekt, H.V. Huikuri, Electrocardiogram as a predictor of sudden cardiac death in middle-aged subjects without a known cardiac disease, Int. J. Cardiol. Heart Vasc. 20 (2018 Aug 26) 50–55, https://doi.org/10.1016/j.ijcha.2018.08.002.

[15] A. Pelliccia, L. De Martino, C. Borrazzo, A. Serdoz, E. Lemme, A. Zorzi, D. Corrado, Clinical correlates and outcome of the patterns of premature ventricular beats in Olympic athletes: a long-term follow-up study, Eur. J. Prev. Cardiol. 28 (2021) 1038–1047, https://doi.org/10.1177/2047487320928452.

[16] A. Di Florio, C. Fusi, F. Anselmi, L. Cavigli, M. Focardi, M. Cameli, A. Felici, M. Capitani, S. Valente, M. Bonifazi, A. Zorzi, D. Corrado, S. Mondillo, F. D'Ascenzi, Clinical management of young competitive athletes with premature ventricular beats: a prospective cohort study, Int. J. Cardiol. 330 (2021 May 1) 59–64, https://doi.org/10.1016/j.ijcard.2021.02.021.

[17] J.A. Drezner, S. Sharma, A. Baggish, M. Papadakis, M.G. Wilson, J.M. Prutkin, A. Gerche, M.J. Ackerman, M. Borjesson, J.C. Salerno, I.M. Asif, D.S. Owens, E. H. Chung, M.S. Emery, V.F. Froelicher, H. Heidbuchel, C. Adamuz, C.A. Asplund, G. Cohen, K.G. Harmon, J.C. Marek, S. Molossi, J. Niebauer, H.F. Pelto, M.V. Perez, N.R. Riding, T. Saarel, C.M. Schmied, D.M. Shipon, R. Stein, V.L. Vetter, A. Pelliccia, D. Corrado, International criteria for electrocardiographic interpretation in athletes: consensus statement, Br. J. Sports Med. 51 (9) (2017 May) 704–731, https://doi.org/10.1136/bjsports-2016-097331.

[18] R. Bastiaenen, A. Pantazis, H. Gonna, I. Chis-Ster, S. Castelletti, V.N. Batchvarov, G. Domenichini, F. Coccolo, G. Boriani, W.J. McKenna, E.R. Behr, M.M. Gallagher, The ventricular ectopic QRS interval (VEQSI): diagnosis of arrhythmogenic right ventricular cardiomyopathy in patients with incomplete disease expression, Heart Rhythm. 13 (7) (2016 Jul) 1504–1512, https://doi.org/10.1016/j.hrthm.2016.03.039.

[19] J. Novak, A. Zorzi, S. Castelletti, A. Pantasis, I. Rigato, D. Corrado, W. Mckenna, P. D. Lambiase, Electrocardiographic differentiation of idiopathic right ventricular outflow tract ectopy from early arrhythmogenic right ventricular cardiomyopathy, Europace. 19 (4) (2017 Apr 1) 622–628, https://doi.org/10.1093/europace/euw018.

[20] Z. Palamà, M. Nesti, A.G. Robles, A. Scarà, S. Romano, E. Cavarretta, M. Penco, P. Delise, M. Rillo, L. Calò, L. Sciarra, Tailoring the ablative strategy for atrial fibrillation: a state-of-the-art review, Cardiol. Res. Pract. 2022 (2022 Feb 28), https://doi.org/10.1155/2022/9295326, 9295326.

[21] P. Delise, G. Allocca, E. Marras, C. Giustetto, F. Gaita, L. Sciarra, L. Calo, A. Proclemer, M. Marziali, L. Rebellato, G. Berton, L. Coro, N. Sitta, Risk stratification in individuals with the Brugada type 1 ECG pattern without previous cardiac arrest: usefulness of a combined clinical and electrophysiologic approach, Eur. Heart J. 32 (2) (2011 Jan) 169–176, https://doi.org/10.1093/eurheartj/ehq381.

[22] V. Russo, P.C. Pafundi, A. Caturano, G. Dendramis, A.O. Ghidini, V.E. Santobuono, L. Sciarra, P. Notarstefano, M.A. Rucco, E. Attena, R. Floris, E. Romeo, B. Sarubbi, G. Nigro, A. D'Onofrio, L. Calò, M. Nesti, Electrophysiological study prognostic value and long-term outcome in drug-induced type 1 Brugada syndrome: the IBRYD study, JACC Clin. Electrophysiol. 7 (10) (2021 Oct) 1264–1273, https://doi.org/10.1016/j.jacep.2021.03.010.

[23] A. Gasperetti, R.T. Carrick, S. Costa, P. Compagnucci, L.P. Bosman, M. Chivulescu, C. Tichnell, B. Murray, H. Tandri, R. Tadros, L. Rivard, M.P. van den Berg, K. Zeppenfeld, A.A.M. Wilde, G. Pompilio, C. Carbucicchio, A. Dello Russo, M. Casella, A. Svensson, C.B. Brunckhorst, J.P. van Tintelen, P.G. Platonov, K. H. Haugaa, F. Duru, A.S.J.M. Te Riele, P. Khairy, C. Tondo, H. Calkins, C.A. James, A.M. Saguner, J. Cadrin-Tourigny, Programmed ventricular stimulation as an additional primary prevention risk stratification tool in Arrhythmogenic right ventricular cardiomyopathy: a multinational study, Circulation. 146 (19) (2022) 1434–1443, https://doi.org/10.1161/CIRCULATIONAHA.122.060866.

[24] J.J. Goldberger, H. Subacius, T. Patel, R. Cunnane, A.H. Kadish, Sudden cardiac death risk stratification in patients with nonischemic dilated cardiomyopathy, J. Am. Coll. Cardiol. 63 (2014) 1879–1889, https://doi.org/10.1016/j.jacc.2013.12.021.

[25] P.M. Elliott, A. Anastasakis, M.A. Borger, M. Borggrefe, F. Cecchi, P. Charron, A. A. Hagege, A. Lafont, G. Limongelli, H. Mahrholdt, W.J. McKenna, J. Mogensen, P. Nihoyannopoulos, S. Nistri, P.G. Pieper, B. Pieske, C. Rapezzi, F.H. Rutten, C. Tillmanns, H. Watkins, 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. 35 (2014) 2733–2779, https://doi.org/10.1093/eurheartj/ehu284.
[26] S.A. Ben-Haim, D. Osadchy, I. Schuster, et al., Nonfluoroscopic, in vivo navigation and mapping technology, Nat. Med. 2 (12) (1996) 1393–1395, https://doi.org/10.1038/nm1296-1393.
[27] J.L. Smeets, S.A. Ben-Haim, L.M. Rodriguez, et al., New method for nonfluoroscopic endocardial mapping in humans: accuracy assessment and first clinical results, Circulation. 97 (24) (1998) 2426–2432, https://doi.org/10.1161/01.cir.97.24.2426.
[28] L. Gepstein, S.J. Evans, Electroanatomical mapping of the heart: basic concepts and implications for the treatment of cardiac arrhythmias, Pacing Clin. Electrophysiol. 21 (6) (1998 Jun) 1268–1278, https://doi.org/10.1111/j.1540-8159.1998.tb00187.x.
[29] R. Kornowski, M.K. Hong, L. Gepstein, S. Goldstein, S. Ellahham, S.A. Ben-Haim, M.B. Leon, Preliminary animal and clinical experiences using an electromechanical endocardial mapping procedure to distinguish infarcted from healthy myocardium, Circulation. 98 (11) (1998 Sep 15) 1116–1124, https://doi.org/10.1161/01.cir.98.11.1116.
[30] H.H. Hsia, D.J. Callans, F.E. Marchlinski, Characterization of endocardial electrophysiological substrate in patients with nonischemic cardiomyopathy and monomorphic ventricular tachycardia, Circulation. 108 (6) (2003) 704–710, https://doi.org/10.1161/01.CIR.0000083725.72693.EA.
[31] D. Corrado, C. Basso, L. Leoni, B. Tokajuk, B. Bauce, G. Frigo, G. Tarantini, M. Napodano, P. Turrini, A. Ramondo, L. Daliento, A. Nava, G. Buja, S. Iliceto, G. Thiene, Three-dimensional electroanatomic voltage mapping increases accuracy of diagnosing arrhythmogenic right ventricular cardiomyopathy/dysplasia, Circulation. 111 (23) (2005 Jun 14) 3042–3050, https://doi.org/10.1161/CIRCULATIONAHA.104.486977.
[32] F. Migliore, A. Zorzi, M. Silvano, M. Bevilacqua, L. Leoni, M.P. Marra, M. Elmaghawry, L. Brugnaro, C. Dal Lin, B. Bauce, I. Rigato, G. Tarantini, C. Basso, G. Buja, G. Thiene, S. Iliceto, D. Corrado, Prognostic value of endocardial voltage mapping in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia, Circ. Arrhythm. Electrophysiol. 6 (1) (2013) 167–176, https://doi.org/10.1161/CIRCEP.111.974881.
[33] A.P. Wijnmaalen, R.J. van der Geest, C.F. van Huls Van Taxis, H.M. Siebelink, L. J. Kroft, J.J. Bax, J.H. Reiber, M.J. Schalij, K. Zeppenfeld, Head-to-head comparison of contrast-enhanced magnetic resonance imaging and electroanatomical voltage mapping to assess post-infarct scar characteristics in patients with ventricular tachycardias: real-time image integration and reversed registration, Eur. Heart J. 32 (1) (2011) 104–114, https://doi.org/10.1093/eurheartj/ehq345.
[34] M.P. Marra, L. Leoni, B. Bauce, F. Corbetti, A. Zorzi, F. Migliore, M. Silvano, I. Rigato, F. Tona, G. Tarantini, L. Cacciavillani, C. Basso, G. Buja, G. Thiene, S. Iliceto, D. Corrado, Imaging study of ventricular scar in arrhythmogenic right ventricular cardiomyopathy: comparison of 3D standard electroanatomical voltage mapping and contrast-enhanced cardiac magnetic resonance, Circ. Arrhythm. Electrophysiol. 5 (1) (2012 Feb) 91–100, https://doi.org/10.1161/CIRCEP.111.964635.
[35] S. Kucukseymen, H. Yavin, M. Barkagan, J. Jang, A. Shapira-Daniels, J. Rodriguez, D. Shim, F. Pashakhanloo, P. Pierce, L. Botzer, W.J. Manning, E. Anter, R. Nezafat, Discordance in scar detection between electroanatomical mapping and cardiac Mri in an infarct swine model, JACC Clin. Electrophysiol. 6 (11) (2020) 1452–1464, https://doi.org/10.1016/j.jacep.2020.08.033. PMID: 33121675.Narducci ML, Pelargonio G, La Rosa G et al. Role of extensive diagnostic workup in young athletes and nonathletes with complex ventricular arrhythmias. Heart Rhythm. 2020;17(2):230–237. doi: 10.1016/j.hrthm.2019.08.022.
[36] P. Santangeli, C. Hamilton-Craig, A. Dello Russo, M. Pieroni, M. Casella, G. Pelargonio, L. Di Biase, C. Smaldone, S. Bartoletti, M.L. Narducci, C. Tondo, F. Bellocci, A. Natale, Imaging of scar in patients with ventricular arrhythmias of right ventricular origin: cardiac magnetic resonance versus electroanatomic mapping, J. Cardiovasc. Electrophysiol. 22 (12) (2011) 1359–1366, https://doi.org/10.1111/j.1540-8167.2011.02127.x.
[37] E.M. Cronin, F.M. Bogun, P. Maury, P. Peichl, M. Chen, N. Namboodiri, L. Aguinaga, L.R. Leite, S.M. Al-Khatib, E. Anter, A. Berruezo, D.J. Callans, M. K. Chung, P. Cuculich, A. d'Avila, B.J. Deal, P. Della Bella, T. Deneke, T. M. Dickfeld, C. Hadid, H.M. Haqqani, G.N. Kay, R. Latchamsetty, F. Marchlinski, J. M. Miller, A. Nogami, A.R. Patel, R.K. Pathak, L.C. Sáenz Morales, P. Santangeli, J. L. Sapp, A. Sarkozy, K. Soejima, W.G. Stevenson, U.B. Tedrow, W.S. Tzou, N. Varma, K. Zeppenfeld, ESC Scientific Document Group, 2019 HRS/EHRA/APHRS/LAHRS expert consensus statement on catheter ablation of ventricular arrhythmias, Europace 21 (8) (2019 Aug 1) 1143–1144, https://doi.org/10.1093/europace/euz132. Erratum in: Europace. 2019 Aug 1;21(8):1144. Erratum in: J Arrhythm. 2020 Jan 12;36(1):214. Erratum in: Europace. 2020 Mar 1;22(3):505. PMID: 31075787; PMCID: PMC7967791.
[38] M. Takigawa, J. Relan, T. Kitamura, C.A. Martin, S. Kim, R. Martin, G. Cheniti, K. Vlachos, G. Massoullié, A. Frontera, N. Thompson, M. Wolf, F. Bourier, A. Lam, J. Duchateau, T. Pambrun, A. Denis, N. Derval, X. Pillois, J. Magat, J. Naulin, M. Merle, F. Collot, B. Quesson, H. Cochet, M. Hocini, M. Haïssaguerre, F. Sacher, P. Jaïs, Impact of spacing and orientation on the scar threshold with a high-density grid catheter, Circ. Arrhythm. Electrophysiol. 12 (9) (2019 Sep), https://doi.org/10.1161/CIRCEP.119.007158 e007158. (Epub 2019 Aug 26. PMID: 31446771).
[39] D. Krum, A. Goel, J. Hauck, J. Schweitzer, J. Hare, M. Attari, A. Dhala, R. Cooley, M. Akhtar, J. Sra, Catheter location, tracking, cardiac chamber geometry creation, and ablation using cutaneous patches, J. Interv. Card. Electrophysiol. 12 (1) (2005 Jan) 17–22, https://doi.org/10.1007/s10840-005-5837-y (PMID: 15717148).
[40] H. Nakagawa, A. Ikeda, T. Sharma, R. Lazzara, W.M. Jackman, Rapid high resolution electroanatomical mapping: evaluation of a new system in a canine atrial linear lesion model, Circ. Arrhythm. Electrophysiol. 5 (2) (2012 Apr) 417–424, https://doi.org/10.1161/CIRCEP.111.968602.
[41] A. Dello Russo, P. Compagnucci, M. Casella, A. Gasperetti, S. Riva, M.A. Dessanai, F. Pizzamiglio, V. Catto, F. Guerra, G. Stronati, D. Andreini, G. Pontone, A. Bonomi, S. Rizzo, L. Di Biase, A. Capucci, A. Natale, C. Basso, C. Fiorentini, P. Zeppilli, C. Tondo, Ventricular arrhythmias in athletes: role of a comprehensive diagnostic workup, Heart Rhythm. 19 (1) (2022 Jan) 90–99, https://doi.org/10.1016/j.hrthm.2021.09.013.
[42] M.E. Josephson, E. Anter, Substrate mapping for ventricular tachycardia: assumptions and misconceptions, JACC Clin. Electrophysiol. 1 (5) (2015 Oct) 341–352, https://doi.org/10.1016/j.jacep.2015.09.001. Epub 2015 Sep 10. PMID: 29759461.
[43] L. Sciarra, Z. Palamà, M. Nesti, C. Lanzillo, M. Di Roma, E. De Ruvo, A.G. Robles, E. Cavarretta, A. Scarà, L. De Luca, D. Grieco, M. Rillo, S. Romano, R. Petroni, M. Penco, L. Calò, Contact-force monitoring increases accuracy of right ventricular voltage mapping avoiding "false scar" detection in patients with no evidence of structural heart disease, Indian Pacing Electrophysiol. J. 20 (6) (2020 Nov-Dec) 243–249, https://doi.org/10.1016/j.ipej.2020.07.004.
[44] F.E. Marchlinski, D.J. Callans, C.D. Gottlieb, E. Zado, Linear ablation lesions for control of unmappable ventricular tachycardia in patients with ischemic and nonischemic cardiomyopathy, Circulation. 101 (11) (2000 Mar 21) 1288–1296, https://doi.org/10.1161/01.cir.101.11.1288 (PMID: 10725289).
[45] S. Kumar, S.H. Baldinger, S. Kapur, J. Romero, N.K. Mehta, S. Mahida, A. Fujii, U. B. Tedrow, W.G. Stevenson, Right ventricular scar-related ventricular tachycardia in nonischemic cardiomyopathy: electrophysiological characteristics, mapping, and ablation of underlying heart disease, J. Cardiovasc. Electrophysiol. 29 (1) (2018 Jan) 79–89, https://doi.org/10.1111/jce.13346.
[46] G.M. Polin, H. Haqqani, W. Tzou, M.D. Hutchinson, F.C. Garcia, D.J. Callans, E. S. Zado, F.E. Marchlinski, Endocardial unipolar voltage mapping to identify epicardial substrate in arrhythmogenic right ventricular cardiomyopathy/dysplasia, Heart Rhythm. 8 (1) (2011) 76–83, https://doi.org/10.1016/j.hrthm.2010.09.088.
[47] M.D. Hutchinson, E.P. Gerstenfeld, B. Desjardins, R. Bala, M.P. Riley, F.C. Garcia, S. Dixit, D. Lin, W.S. Tzou, J.M. Cooper, R.J. Verdino, D.J. Callans, F. E. Marchlinski, Endocardial unipolar voltage mapping to detect epicardial ventricular tachycardia substrate in patients with nonischemic left ventricular cardiomyopathy, Circ. Arrhythm. Electrophysiol. 4 (1) (2011) 49–55, https://doi.org/10.1161/CIRCEP.110.959957.
[48] C.A. Glashan, A.F.A. Androulakis, Q. Tao, R.N. Glashan, L.J. Wisse, M. Ebert, M. C. de Ruiter, B.J. van Meer, C. Brouwer, O.M. Dekkers, D.A. Pijnappels, J.M.T. de Bakker, M. de Riva, S.R.D. Piers, K. Zeppenfeld, Whole human heart histology to validate electroanatomical voltage mapping in patients with non-ischaemic cardiomyopathy and ventricular tachycardia, Eur. Heart J. 39 (31) (2018) 2867–2875, https://doi.org/10.1093/eurheartj/ehy168.
[49] J.M. de Bakker, F.J. van Capelle, M.J. Janse, S. Tasseron, J.T. Vermeulen, N. de Jonge, J.R. Lahpor, Slow conduction in the infarcted human heart. 'Zigzag' course of activation, Circulation. 88 (3) (1993) 915–926, https://doi.org/10.1161/01.cir.88.3.915 (PMID: 8353918).
[50] S.E. Mountantonakis, R.E. Park, D.S. Frankel, M.D. Hutchinson, S. Dixit, J. Cooper, D. Callans, F.E. Marchlinski, E.P. Gerstenfeld, Relationship between voltage map "channels" and the location of critical isthmus sites in patients with post-infarction cardiomyopathy and ventricular tachycardia, J. Am. Coll. Cardiol. 61 (20) (2013) 2088–2095, https://doi.org/10.1016/j.jacc.2013.02.031.
[51] D. Zachariah, K. Nakajima, L.R. Limite, D. Zweiker, M. Spartalis, D. Zirolia, M. Musto, G. D'Angelo, G. Paglino, F. Baratto, M. Cireddu, C. Bisceglia, A. Radinovic, A. Marzi, S. Sala, G. Peretto, P. Vergara, S. Gulletta, P. Mazzone, P. Della Bella, A. Frontera, Significance of abnormal and late ventricular signals in ventricular tachycardia ablation of ischemic and nonischemic cardiomyopathies, Heart Rhythm. S1547-5271 (22) (2022) 02293–02297, https://doi.org/10.1016/j.hrthm.2022.08.008.
[52] M. de Riva, Y. Naruse, M. Ebert, A.F.A. Androulakis, Q. Tao, M. Watanabe, A. P. Wijnmaalen, J. Venlet, C. Brouwer, S.A. Trines, M.J. Schalij, K. Zeppenfeld, Targeting the hidden substrate unmasked by right ventricular Extrastimulation improves ventricular tachycardia ablation outcome after myocardial infarction, JACC Clin. Electrophysiol. 4 (3) (2018) 316–327, https://doi.org/10.1016/j.jacep.2018.01.013.
[53] E. Anter, C.M. Tschabrunn, A.E. Buxton, M.E. Josephson, High-resolution mapping of Postinfarction reentrant ventricular tachycardia: electrophysiological characterization of the circuit, Circulation. 134 (4) (2016) 314–327, https://doi.org/10.1161/CIRCULATIONAHA.116.021955.
[54] E. Leshem, C.M. Tschabrunn, J. Jang, J. Whitaker, I. Zilberman, C. Beeckler, A. Govari, J. Kautzner, P. Peichl, R. Nezafat, E. Anter, High-resolution mapping of ventricular scar: evaluation of a novel integrated multielectrode mapping and ablation catheter, JACC Clin. Electrophysiol. 3 (3) (2017) 220–231, https://doi.org/10.1016/j.jacep.2016.12.016.
[55] C.A. Glashan, H.K.C. Beukers, B.J. Tofig, Q. Tao, S. Blom, B. Mertens, S. B. Kristiansen, K. Zeppenfeld, Mini-, Micro-, and conventional electrodes: an in vivo electrophysiology and ex vivo histology head-to-head comparison, JACC Clin. Electrophysiol. 7 (2) (2021) 197–205, https://doi.org/10.1016/j.jacep.2020.08.014.
[56] A. Dello Russo, P. Compagnucci, M. Bergonti, L. Cipolletta, Q. Parisi, G. Volpato, G. Santarelli, M. Colonnelli, J. Saenen, Y. Valeri, L. Carboni, P. Marchese, M. Marini, A. Sarkozy, A. Natale, M. Casella, Microelectrode voltage mapping for substrate assessment in catheter ablation of ventricular tachycardia: a dual-center

experience, J. Cardiovasc. Electrophysiol. (2023), https://doi.org/10.1111/jce.15908 in press.
[57] S. Castelletti, A. Zorzi, E. Ballardini, C. Basso, A. Biffi, F. Brancati, E. Cavarretta, L. Crotti, M. Contursi, A. D'Aleo, F. D'Ascenzi, P. Delise, A. Dello Russo, G. Gazale, L. Mos, V. Novelli, Z. Palamà, S. Palermi, V. Palmieri, G. Patrizi, A. Pelliccia, K. Pilichou, S. Romano, P. Sarto, P.J. Schwartz, M. Tiberi, P. Zeppilli, D. Corrado, L. Sciarra, Molecular genetic testing in athletes: why and when a position statement from the Italian Society of Sports Cardiology, Int. J. Cardiol. 364 (2022) 169–177, https://doi.org/10.1016/j.ijcard.2022.05.071.
[58] M. Casella, F. Pizzamiglio, A. Dello Russo, C. Carbucicchio, G. Al-Mohani, E. Russo, P. Notarstefano, M. Pieroni, G. D'Amati, E. Sommariva, M. Giovannardi, A. Carnevali, S. Riva, G. Fassini, F. Tundo, P. Santangeli, L. Di Biase, L. Bolognese, A. Natale, C. Tondo, Feasibility of combined unipolar and bipolar voltage maps to improve sensitivity of endomyocardial biopsy, Circ. Arrhythm. Electrophysiol. 8 (3) (2015) 625–632, https://doi.org/10.1161/CIRCEP.114.002216.
[59] M. Bergonti, M. Casella, P. Compagnucci, A.D. Russo, C. Tondo, Electroanatomic mapping system and Intracardiac-Echo to guide endomyocardial biopsy, Card Electrophysiol. Clin. 13 (2) (2021 Jun) 381–392, https://doi.org/10.1016/j.ccep.2021.02.005.
[60] M. Casella, A. Dello Russo, M. Bergonti, V. Catto, E. Conte, E. Sommariva, A. Gasperetti, G. Vettor, F. Tundo, R. Sicuso, S. Rizzo, S. Mushtaq, D. Della Rocca, G. Pompilio, L. Di Biase, D. Andreini, A. Natale, C. Basso, C. Tondo, Diagnostic yield of Electroanatomic voltage mapping in guiding endomyocardial biopsies, Circulation. 142 (13) (2020 Sep 29) 1249–1260, https://doi.org/10.1161/CIRCULATIONAHA.120.046900.
[61] M. Casella, A. Dello Russo, M. Bergonti, V. Catto, E. Conte, E. Sommariva, A. Gasperetti, G. Vettor, F. Tundo, R. Sicuso, S. Rizzo, S. Mushtaq, D. Della Rocca, G. Pompilio, L. Di Biase, D. Andreini, A. Natale, C. Basso, C. Tondo, Endomyocardial Biopsy: The Forgotten Piece in the Arrhythmogenic Cardiomyopathy Puzzle, J. Am. Heart Assoc. 10 (19) (2021 Oct 5), https://doi.org/10.1161/JAHA.121.021370 e021370. Epub 2021 Sep 25. PMID: 34569251; PMCID: PMC8649151.
[62] P.M. Seferović, H. Tsutsui, D.M. McNamara, A.D. Ristić, C. Basso, B. Bozkurt, L. T. Cooper Jr., G. Filippatos, T. Ide, T. Inomata, K. Klingel, A. Linhart, A.R. Lyon, M. R. Mehra, M. Polovina, I. Milinković, K. Nakamura, S.D. Anker, I. Veljić, T. Ohtani, T. Okumura, T. Thum, C. Tschöpe, G. Rosano, A.J.S. Coats, R.C. Starling, Heart failure association of the ESC, Heart Failure Society of America and Japanese heart failure society position statement on endomyocardial biopsy, Eur. J. Heart Fail. 23 (6) (2021) 854–871, https://doi.org/10.1002/ejhf.2190.
[63] F. Zoppo, G. Gagno, L. Perazza, A. Cocciolo, G. Mugnai, D. Vaccari, V. Calzolari, Electroanatomic voltage mapping and characterisation imaging for "right ventricle arrhythmic syndromes" beyond the arrhythmia definition: a comprehensive review, Int. J. Card. Imaging 37 (8) (2021) 2347–2357, https://doi.org/10.1007/s10554-021-02221-3.
[64] K. Zeppenfeld, J. Tfelt-Hansen, M. de Riva, B.G. Winkel, E.R. Behr, N.A. Blom, P. Charron, D. Corrado, N. Dagres, C. de Chillou, L. Eckardt, T. Friede, K. H. Haugaa, M. Hocini, P.D. Lambiase, E. Marijon, J.L. Merino, P. Peichl, S.G. Priori, T. Reichlin, J. Schulz-Menger, C. Sticherling, S. Tzeis, A. Verstrael, M. Volterrani, ESC Scientific Document Group, 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, Eur. Heart J. 43 (40) (2022) 3997–4126, https://doi.org/10.1093/eurheartj/ehac262.
[65] M. Casella, A. Gasperetti, P. Compagnucci, M.L. Narducci, G. Pelargonio, V. Catto, C. Carbucicchio, G. Bencardino, E. Conte, N. Schicchi, D. Andreini, G. Pontone, A. Giovagnoni, S. Rizzo, F. Inzani, C. Basso, A. Natale, C. Tondo, A.D. Russo, F. Crea, Different phases of disease in lymphocytic myocarditis: clinical and electrophysiological characteristics, JACC: Clin. Electrophysiol. 9 (3) (2023) 314–326, https://doi.org/10.1016/j.jacep.2022.10.004. Epub 2022 Nov 30. PMID: 36752480.
[66] J. Venlet, S.R. Piers, J.D. Jongbloed, A.F. Androulakis, Y. Naruse, D.W. den Uijl, G. F. Kapel, M. de Riva, J.P. van Tintelen, D.Q. Barge-Schaapveld, M.J. Schalij, K. Zeppenfeld, Isolated Subepicardial right ventricular outflow tract scar in athletes with ventricular tachycardia, J. Am. Coll. Cardiol. 69 (5) (2017 Feb 7) 497–507, https://doi.org/10.1016/j.jacc.2016.11.041 (PMID: 28153106).
[67] G. Brunetti, A. Cipriani, M. Perazzolo Marra, M. De Lazzari, B. Bauce, C. Calore, I. Rigato, F. Graziano, R. Vio, D. Corrado, A. Zorzi, Role of cardiac magnetic resonance imaging in the evaluation of athletes with premature ventricular beats, J. Clin. Med. 11 (2) (2022 Jan 14) 426, https://doi.org/10.3390/jcm11020426. PMID: 35054118; PMCID: PMC8781801.
[68] P. Compagnucci, G. Volpato, U. Falanga, L. Cipolletta, M.A. Conti, G. Grifoni, G. Ciliberti, G. Stronati, M. Fogante, M. Bergonti, E. Sommariva, F. Guerra, A. Giovagnoni, A. Dello Russo, M. Casella, Myocardial inflammation, sports practice, and sudden cardiac death: 2021 update, Medicina (Kaunas) 57 (3) (2021) 277, https://doi.org/10.3390/medicina57030277. PMID: 33802881; PMCID: PMC8002711.
[69] G. Peretto, S. Sala, C. Basso, Bella P. Della, Programmed ventricular stimulation in patients with active vs previous arrhythmic myocarditis, J. Cardiovasc. Electrophysiol. 31 (3) (2020) 692–701, https://doi.org/10.1111/jce.14374. Epub 2020 Feb 3. PMID: 31999020.
[70] A. Zorzi, N. Bettella, M. Tatangelo, A. Del Monte, T. Vessella, B. Poscolieri, C. Crescenzi, D. Pegorin, F. D'Ascenzi, V. Pescatore, F. Giada, P. Sarto, L. Calò, M. Schiavon, D. Gregori, D.M. Hadley, J.A. Drezner, A. Pelliccia, D. Corrado, Prevalence and clinical significance of isolated low QRS voltages in young athletes, Europace. (2022 Mar 4), https://doi.org/10.1093/europace/euab330 euab330.
[71] G. Peretto, M. Casella, M. Merlo, S. Benedetti, S. Rizzo, C. Cappelletto, C. Di Resta, P. Compagnucci, M. De Gaspari, A. Dello Russo, G. Casari, C. Basso, S. Sala, G. Sinagra, P. Della Bella, L.T. Cooper Jr., Inflammation on endomyocardial biopsy predicts risk of MACE in undefined left ventricular Arrhythmogenic cardiomyopathy, JACC Clin. Electrophysiol. (2022), https://doi.org/10.1016/j.jacep.2022.10.032. S2405-500X(22)00949–5.
[72] G. Peretto, S. Sala, G. De Luca, R. Marcolongo, C. Campochiaro, S. Sartorelli, M. Tresoldi, L. Foppoli, A. Palmisano, A. Esposito, F. De Cobelli, S. Rizzo, G. Thiene, C. Basso, L. Dagna, A.L.P. Caforio, Bella P. Della, Immunosuppressive therapy and risk stratification of patients with myocarditis presenting with ventricular arrhythmias, JACC Clin. Electrophysiol. 6 (10) (2020) 1221–1234, https://doi.org/10.1016/j.jacep.2020.05.013.