Ventricular arrhythmias in athletes: Role of a comprehensive diagnostic workup

Antonio Dello Russo, MD, PhD,[*†1] Paolo Compagnucci, MD,[*†1] Michela Casella, MD, PhD,[*‡] Alessio Gasperetti, MD,[*†§¶] Stefania Riva, MD,[§] Maria Antonietta Dessanai, MD,[§] Francesca Pizzamiglio, MD,[§] Valentina Catto, PhD,[§] Federico Guerra, MD,[*†] Giulia Stronati, MD,[*†] Daniele Andreini, MD PhD,[§‖] Gianluca Pontone, MD, PhD,[§] Alice Bonomi, PhD,[§] Stefania Rizzo, MD,[**] Luigi Di Biase, MD, PhD,[††] Alessandro Capucci, MD,[*†] Andrea Natale, MD,[‡‡] Cristina Basso, MD, PhD,[**] Cesare Fiorentini, MD,[§] Paolo Zeppilli, MD,[§§] Claudio Tondo, MD, PhD[§‖]

*From the *Cardiology And Arrhythmology Clinic, University Hospital "Ospedali Riuniti", Ancona, Italy, †Department of Biomedical Sciences and Public Health, Marche Polytechnic University, Ancona, Italy, ‡Department of Clinical, Special and Dental Sciences, Marche Polytechnic University, Ancona, Italy, §Centro Cardiologico Monzino IRCCS, Milan, Italy, ¶University Heart Center, University Hospital Zurich, Zurich, Switzerland, ‖Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, **Department of Cardiac Thoracic and Vascular Sciences and Public Health, University of Padua Medical School, Padua, Italy, ††Albert Einstein College of Medicine at Montefiore Hospital, New York, New York, ‡‡Texas Cardiac Arrhythmia Institute, St. David's Medical Center, Austin, Texas, and §§Department of Cardiology and Sports Medicine Institute, Catholic University of the Sacred Heart, Rome, Italy.*

BACKGROUND Ventricular arrhythmias (VAs) represent a critical issue with regard to sports eligibility assessment in athletes. The ideal diagnostic evaluation of competitive and leisure-time athletes with complex VAs has not been clearly defined.

OBJECTIVE The purpose of this study was to assess the clinical implications of invasive electrophysiological assessments and endomyocardial biopsy (EMB) among athletes with VAs.

METHODS We evaluated 227 consecutive athletes who presented to our institutions after being disqualified from participating in sports because of VAs. After noninvasive tests, electrophysiological study (EPS), electroanatomic mapping (EAM), and EAM- or cardiac magnetic resonance imaging–guided EMB was performed, following a prespecified protocol. Sports eligibility status was redefined at 6-month follow-up.

RESULTS From our sample, 188 athletes (82.8%) underwent EAM and EPS, and 42 (15.2%) underwent EMB. A diagnosis of heart disease could be formulated in 30% of the study population (67/227; 95% confidence interval [CI] 0.24–0.36) after noninvasive tests; in 37% (83/227; 95% CI 31%–43%) after EPS and EAM; and in 45% (102/227; 95% CI 39%–51%) after EMB. In the subset of athletes undergoing EMB, invasive diagnostic workup allowed diagnostic reclassification of half of the athletes (n = 21 [50%]). Reclassification was particularly common among subjects without definitive findings after noninvasive evaluation (n = 23; 87% reclassified). History of syncope, abnormal echocardiogram, presence of late gadolinium enhancement, and abnormal EAM were linked to sports ineligibility at 6-month follow-up.

CONCLUSION A comprehensive invasive workup provided additional diagnostic elements and could improve the sports eligibility assessment of athletes presenting with VAs. The extensive invasive evaluation presented could be especially helpful when noninvasive tests show unclear findings.

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Introduction

Athletes presenting with ventricular arrhythmias (VAs) are a challenge for physicians, often resulting in management uncertainties. Some forms of VAs, such as premature ventricular complexes (PVCs) and nonsustained ventricular tachycardias (NSVTs), have been considered a feature of the athlete's heart adaptive phenotype[1] and tend to disappear after a brief period of detraining.[2]

However, VAs also may represent the main clinical clue to a concealed cardiomyopathy, potentially heralding sudden cardiac death (SCD) during strenuous physical exercise.[3–5] Recently, invasive assessments including 3-dimensional electroanatomic mapping (EAM) and EAM-guided endomyocardial biopsy (EMB) have emerged as reliable tools to better characterize the underlying myocardial substrate in patients presenting with VAs.[3,5,6]

Whether invasive tests aid in the management and definition of sports eligibility status of athletes with VAs currently is uncertain. We sought to evaluate the role of a comprehensive diagnostic workup among competitive or leisure-time athletes who were denied sports eligibility because of VAs.

Methods

Study population

This was a dual-center, retrospective analysis of prospectively enrolled patients. From February 2010 to September 2019, 227 consecutive competitive athletes who were disqualified from participating in competitive or leisure-time sports because of NSVTs, sustained ventricular tachycardias (SVTs), frequent (>500 per day) or exercise-related PVCs of any morphology detected by electrocardiographic (ECG) monitoring or exercise stress testing, or resuscitated ventricular fibrillation (VF) were evaluated at the Heart Rhythm Center, Monzino Cardiology Center, IRCCS, Milan, Italy, and at the Cardiology and Arrhythmology Clinic, University

Figure 1 Study flowchart. ARVC = arrhythmogenic right ventricular cardiomyopathy; CAD = coronary artery disease; cMRI = cardiac magnetic resonance imaging; CT = computed tomography; EAM = electroanatomic mapping; ECG = electrocardiography; EMB = endomyocardial biopsy; EPS = electrophysiological study.

Hospital "Ospedali Riuniti", Ancona, Italy. The research adhered to the Helsinki Declaration as revised in 2013. The study was approved by an institutional review board, and all patients provided written informed consent. Each subject was evaluated according to a prespecified protocol (Figure 1), which included noninvasive as well as invasive tests (Supplemental Methods).

Noninvasive evaluation and testing for coronary artery disease

The noninvasive evaluation and testing for coronary artery disease are described in Figure 1 and in the Supplemental Methods. After these assessments, a clinical/radiological diagnosis was formulated in a collegial way based on all the available information according to published recommendations and international guidelines,[7–18] as detailed in the Supplemental Methods.

Invasive evaluation

Invasive evaluation included 3-dimensional EAM, electrophysiological study (EPS), and EAM- or cardiac magnetic resonance imaging (cMRI)-guided EMB (Figure 1).

The decision to perform invasive diagnostic evaluations was prespecified by institutional protocol as follows: 3-dimensional EAM and EPS were performed in case of diagnostic doubts after noninvasive tests or, in case of diagnostic certainty after noninvasive tests, as a preliminary step to catheter ablation (CA) procedures.[1,3–6]

EMB was performed in case of persistent diagnostic uncertainty after noninvasive evaluations, EPS, and EAM.[6] If all test results were normal, the decision to proceed to invasive tests including EMB was based on the severity of clinical presentation, reserving the tests for patients who presented with aborted SCD due to unexplained VF.

Furthermore, when myocarditis was clinically suspected, EAM, EPS, and EMB were obtained in order to confirm the diagnosis, assess disease severity and its arrhythmic potential, characterize the type of inflammatory infiltrate, and identify the presence of viral genome.[8] In case of a clinical diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC), the full invasive workup (EAM, EPS, and EMB) was performed in order to obtain an important additional element in the differential diagnosis between ARVC and athlete's heart.[10,14]

In our cohort, invasive diagnostic tests were not performed in all cases in which the tests would have been indicated by protocol, as 11 patients denied consent for EAM, EPS, and EMB, whereas 28 subjects refused EMB (Figure 1) due to concerns about EMB-related adverse events.

Final diagnosis and sports eligibility management

A final diagnosis was collegially formulated in all cases according to the results of both noninvasive and invasive tests, following international guidelines and recommendations.[7–18] A final diagnosis of ARVC was accepted in the presence of a borderline or definite level of diagnosis, in accordance with the 2010 revised International Task Force criteria.[10,14] Specific therapeutic measures were taken accordingly, including CA and implantable cardioverter-defibrillator (ICD), if clinically indicated.[7]

Sports eligibility was reassessed at the end of the diagnostic workup as follows. When a diagnosis of ARVC or mitochondrial cardiomyopathy was formulated, patients were permanently disqualified from participating in competitive or leisure-time sports, according to existing guidelines.[16–18] In case of a diagnosis of myocarditis, patients underwent a 6-month period of detraining followed by diagnostic re-evaluation with gadolinium-enhanced cMRI and 24-hour ECG monitoring.[8] Patients were considered eligible for competitive or leisure-time sports in case of normal findings on cMRI (ie, normal chamber dimensions and function) and absence of complex VAs (ie, < 2000 PVCs/day; absence of NSVT, SVT, and VF) on 24-hour ECG monitoring.[16–18] For patients with dilated cardiomyopathy or left ventricular (LV) noncompaction, a case-by-case evaluation was performed, weighing individual determinants of risk. When a diagnosis of structural heart disease was excluded, sports participation was allowed after a 6-month detraining period in case of absence of complex VAs on follow-up 24-hour ECG monitoring.[16–18]

Table 1 Baseline clinical characteristics

	Overall (n = 227)
Age (y) (IQR)	26 (23)
Male sex	183 (80.6)
Type of sport	
Athletics	60 (26.4)
Soccer	59 (26.0)
Cycling	26 (11.5)
Volleyball	19 (8.4)
Basketball	16 (7.0)
Swimming	11 (4.9)
Rugby	8 (3.5)
Other	28 (12.3)
Index arrhythmia	
Frequent PVCs at rest	157 (69.2)
Exercise-related PVCs	47 (20.7)
Nonsustained VTs	99 (43.6)
Sustained VTs	25 (11)
VF	9 (4)
Level of training	
Leisure-time athlete	51 (22.5)
Competitive athlete	176 (77.5)
Professional athlete	9 (4)
Symptoms	
None	116 (51.1)
Palpitations	82 (36.1)
Syncope	17 (7.5)
Dizziness	25 (11)
Cardiac arrest	7 (3.1)
Family history	
Premature sudden death	9 (4)
Cardiomyopathy	7 (3.1)

Categorical variables are given as n (%).

IQR = interquartile range; PVC = premature ventricular complex; VF = ventricular fibrillation; VT = ventricular tachycardia.

Table 2 Results of noninvasive and invasive tests

	Overall (n = 227)
ECG	
Normal*	151 (66.5)
Borderline*	30 (13.2)
Abnormal*	46 (20.3)
T-wave inversion	33 (14.5)
Right bundle branch block	6 (2.6)
Right-axis deviation	29 (12.8)
Left-axis deviation	8 (3.5)
Exercise stress testing	209 (92.1)
Suppression	66 (31.6)
No arrhythmias	34 (16.3)
VA reduction	16 (7.6)
PVC persistence/induction	51 (24.4)
Nonsustained VT	27 (12.9)
Sustained VT	8 (3.8)
Echocardiogram	
Normal	162 (71.4)
Abnormal	65 (28.6)
LV EF ≤0.50	18 (7.9)
Regional LV WMA	13 (5.7)
Mitral valve prolapse	19 (8.4)
Global RV dysfunction	5 (2.2)
Regional RV WMA	9 (4)
cMRI	213 (93.8)
Normal	97 (45.5)
Abnormal	116 (54.5)
LV EF ≤0.50	28 (13.1)
Regional LV WMA	23 (10.8)
RV EF ≤0.45	19 (8.9)
Regional RV WMA	38 (17.8)
cMRI tissue characterization	
LGE	67 (31.5)
LV LGE	57 (26.8)
LV LGE pattern	
Stria	44 (20.7)
Junctional/spotty	13 (6.1)
LV LGE distribution	
Anterior wall	14 (24.6)
Lateral wall	33 (57.9)
Inferior wall	33 (57.9)
Septum	25 (43.9)
LV apical cap	2 (3.5)
RV LGE	13 (6.1)
RV LGE distribution	
RV free wall	10 (4.7)
RVOT	6 (2.8)
Myocardial fat infiltration	20 (9.4)
EPS	188 (82.8)
Nonsustained VT induction	6 (3.2)
Sustained VT/VF induction	13 (6.9)
EAM	188 (82.8)
Normal	142 (75.5)
Abnormal	46 (24.5)
Low-voltage area/scar	45 (23.9)
Late potentials	12 (6.4)
Mapped ventricle	
RV	154 (81.9)
LV	54 (28.7)
Regional distribution of abnormal findings	
RVOT	16 (10.4)
Subtricuspid RV	12 (7.8)
RV apex	7 (4.5)
LV inferolateral wall	12 (22.2)
LVOT	2 (3.7)

Values are presented as n (%).

cMRI = cardiac magnetic resonance imaging; EAM = electroanatomic mapping; ECG = electrocardiography; EF = ejection fraction; EPS = electrophysiological study; LGE = late gadolinium enhancement; LV = left ventricle; LVOT = left ventricular outflow tract; RV = right ventricle; RVOT = right ventricular outflow tract; VA = ventricular arrhythmia; WMA = Wall-motion abnormality; other abbreviations as in Table 1.

*ECG is defined normal, abnormal, or borderline according to Sharma S, Drezner JA, Baggish A, et al. International recommendations for electrocardiographic interpretation in athletes. J Am Coll Cardiol 2017;69:1057–1075.

Statistical analysis

The Shapiro-Wilk test was used to check continuous variables for normality. Non-normal variables are expressed as median (interquartile range [IQR]), whereas categorical variables are reported as count (percentage). Categorical differences between groups were calculated with the 2-tailed χ^2 or Fisher exact test, as appropriate. To assess the impact of the various diagnostic tests on sports eligibility at 6-month follow-up, univariable and multivariable logistic regression models were built. First, we developed a multivariable model including information derived from history and noninvasive tests. Then, to test whether invasive evaluations were independently related to sports eligibility over and above noninvasive assessments, a second model incorporating results of EPS and EAM in addition to noninvasive variables was created. Diagnostic performance of the 2 nested models was compared with the Wald test. An α level <0.05 was considered statistically significant. RStudio software (RStudio Inc., Boston, MA) was used for statistical analysis.

Results

Patients

Baseline characteristics of the patients are summarized in Table 1. In briefly, the median age of the cohort was 26 years, and 44 of the enrolled athletes (19%) were women. The vast majority of subjects (n = 176 [78%]) were competitive athletes. Frequent PVCs or exercise-related PVCs were the most common VA at presentation (n = 180 [79%]). Approximately half of the athletes were symptomatic (n = 111 [49%]), most commonly for palpitations (n = 82 [36%]), whereas 17 subjects (8%) had a history of syncope. A family history of premature sudden death (n = 9 [4%]) or cardiomyopathy (n = 7 [3%]) was obtained in a minority of athletes.

Noninvasive evaluations and coronary testing

The results of ECG, exercise stress testing, echocardiography, and cMRI in the whole cohort are summarized in Table 2 and described in the Supplemental Results. The results of these tests among athletes undergoing EMB are given in Supplemental Tables 1 and 2.

Clinical/radiological diagnoses

Overall, after noninvasive evaluation, 81 patients had normal findings, and clinically suspected myocarditis was identified in 20 patients. ARVC was clinically diagnosed in 13 patients: 9 with borderline diagnosis and 4 with a definite diagnosis (Figure 2). Other diagnoses were rarer (Figure 2). Diagnostic findings were judged not definitive in one-third of athletes (n = 79 [35%]). Thirty-six of these subjects had cMRI-proven myocardial scarring.

EAM results

The results of EAM and EPS in the whole cohort are summarized in Table 2, and diagnoses before and after EAM and EPS are shown in Figures 2 and 3. Results of invasive tests among patients undergoing EMB are given in Supplemental Table 2. EAM was performed in 188 patients (83%). According to the presumed origin of VA, only the right ventricle (RV) was mapped in 135 patients (72%), and only the LV was mapped in 34 cases (18%). Both ventricles were mapped in 19 athletes (10%).

EAM results were abnormal in 46 patients (24%), with evidence of myocardial scar (n = 45) and/or late potentials (n = 12). Interestingly, 8 patients with RV morphofunctional abnormalities (2 RV bulging; 2 RV fibrofatty infiltration ; 3 possible ARVC; 1 borderline ARVC) had normal RV EAM, consistent with a noncardiomyopathic myocardial substrate. Furthermore, among patients without definitive findings after noninvasive assessments, EAM revealed normal voltages in 49 subjects (67%).

EMB results

EMB results are given in Supplemental Table 2. EMB had good diagnostic yield, enabling formulation of a pathologic diagnosis in 32 athletes (76%).

The most common EMB diagnosis was myocarditis (n = 19 [45.2%]). Our cohort included 8 patients with biopsy-proven acute (active) myocarditis (42.1%) and 11 subjects with chronic myocarditis (57.9%). Although inflammatory infiltrates were lymphocytic in most cases (n = 17 [89.5%]), there also were 1 acute eosinophilic myocarditis and 1 giant-cell chronic myocarditis. Viral genomes were detected in a minority of patients (n = 3 [14%]): 1 with human herpesvirus 6 and 2 with rhinovirus.

In 9 patients (23.8%), EMB disclosed myocyte loss with fibrofatty replacement, consistent with a pathologic diagnosis of ARVC.[10,14] Interestingly, EMB allowed upgrading from a borderline to a definite level of ARVC diagnosis in 5 athletes. Furthermore, ARVC was diagnosed in a patient with radiologically suspected myocarditis and in 3 athletes without definitive findings after noninvasive evaluation. All three of these athletes had cMRI evidence of nonischemic LV scar with a subepicardial inferolateral stria pattern, but no cMRI criteria for a diagnosis of ARVC according to the 2010 recommendations.[10]

Among the 4 remaining athletes, 3 had normal EMB results (7.1%) and completed a disease rule-out, whereas 1 (2.4%) had histologic evidence of massive mitochondrial proliferation, which led to a diagnosis of mitochondrial cardiomyopathy.[15]

Final diagnoses and reclassification

The diagnostic process is shown in Figure 2, and the diagnostic reclassification flow is shown in Figure 3 and Supplemental Figures 1 to 4. The diagnostic reclassification in patients undergoing EMB is shown in Figure 4. Overall, heart disease was diagnosed in 102 patients (45%) in the whole study population. The most common primary conditions identified included myocarditis (n = 33 [15%]), dilated cardiomyopathy (n = 23 [10%]), and ARVC (n = 17 [8%]).

Among subjects undergoing EMB, the most common final diagnoses were myocarditis (n = 21 [50%]) and ARVC (n = 13 [31%]). This latter cardiomyopathy exclusively involved the RV in 6 cases (46%), whereas 5 patients had biventricular involvement (39%), and 2 (15%) had biopsy-proven left-dominant disease.[10,14]

The full invasive workup, including EMB, allowed diagnostic reclassification of 21 athletes (50%) (Figure 3). The subgroup of athletes without definitive findings after noninvasive evaluation (87% reclassified) emerged as particularly prone to diagnostic reclassification. Prevalence of heart disease in our sample passed from 0.3 (95% confidence interval [CI] 0.24–0.36) when only considering noninvasive tests, to 0.37 (95% CI 0.31–0.43) after adding EAM and EPS, to 0.45 (95% CI 39-51%) after EMB. Q4

Even patients with exclusively frequent PVCs at rest (n = 81 [36%]) or NSVTs with/without frequent PVCs at rest (n = 71 [31%]) had a significant prevalence of heart disease at the end of the diagnostic workup (n = 31 [38%] and n = 32 [45%], respectively). Nonetheless, when noninvasive tests (including cMRI) revealed completely normal findings, invasive assessment did not lead to diagnostic reclassification (Figure 3).

EPS, CA, and ICD implantation

After programmed electrical stimulation, SVTs were induced in 11 patients (6%), VF in 2 (1%), NSVTs in 6 (3%), and accelerated idioventricular rhythm in 1 (1%). EPS reproduced clinical VAs in 16 patients (80%), whereas it did not in the remaining 4 (20%). Ajmaline testing performed in 4 cases revealed drug-induced type 1 Brugada pattern in 2 cases, thus resulting in diagnostic reclassification.[7]

CA of VAs was performed in 114 cases (50%), and ICDs were implanted in 20 patients, for primary (n = 12) or secondary (n = 8) prevention of SCD.[7] Invasive diagnostic tests proved valuable in selecting candidates for ICD implantation for the primary prevention of SCD. EPS showed VAs inducibility in 50% (n = 6) and, among the 7 implanted patients undergoing EMB, 3 (42.9%) were reclassified according to pathology reports.

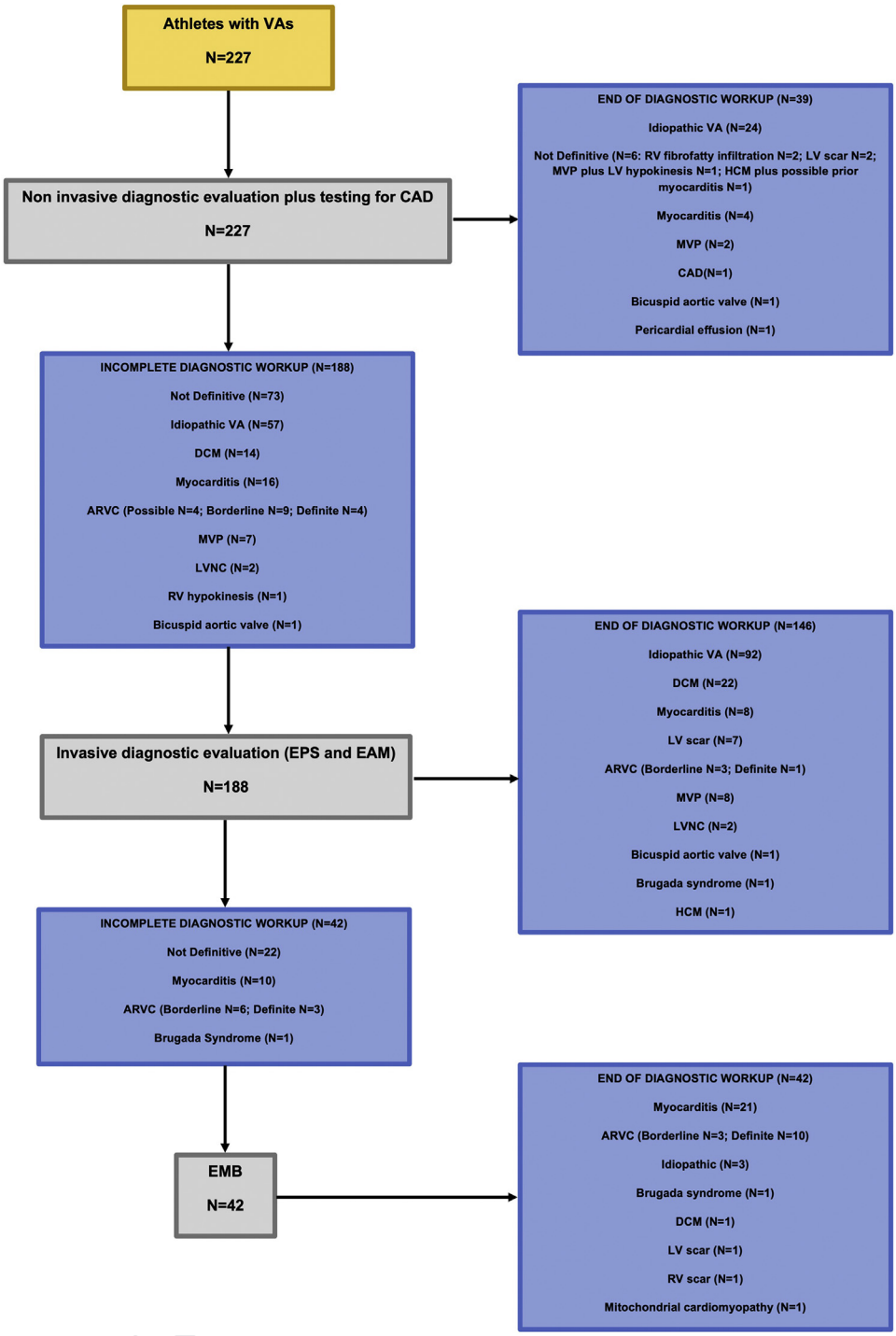

Figure 2 Noninvasive and invasive diagnostic workup and provisional diagnoses. DCM = dilated cardiomyopathy; LV = left ventricle; LVNC = left ventricular noncompaction; MVP = mitral valve prolapse; RV = right ventricle; VA = ventricular arrhythmia; other abbreviations as in Figure 1.

Complications

Seven patients (3%) experienced complications after the invasive procedure: 4 related to femoral vascular access (1 surgically treated femoral pseudoaneurysm and 3 conservatively managed arteriovenous fistulas); 1 self-limited pericardial effusion; 1 ventricular thrombosis; and 1 hepatic hematoma after epicardial CA. Remarkably, no patient undergoing EMB experienced complications.

Sports eligibility reassessment

After 6 months of physical deconditioning, 112 athletes (49%) were allowed to resume participating in competitive sports. In most of these subjects (n = 81 [72%]), heart disease was ruled out after the extensive diagnostic protocol. Fifty subjects (22%) were judged eligible for leisure-time sports activity. The remaining 65 patients (29%) were deemed ineligible. The process of sports eligibility reassessment

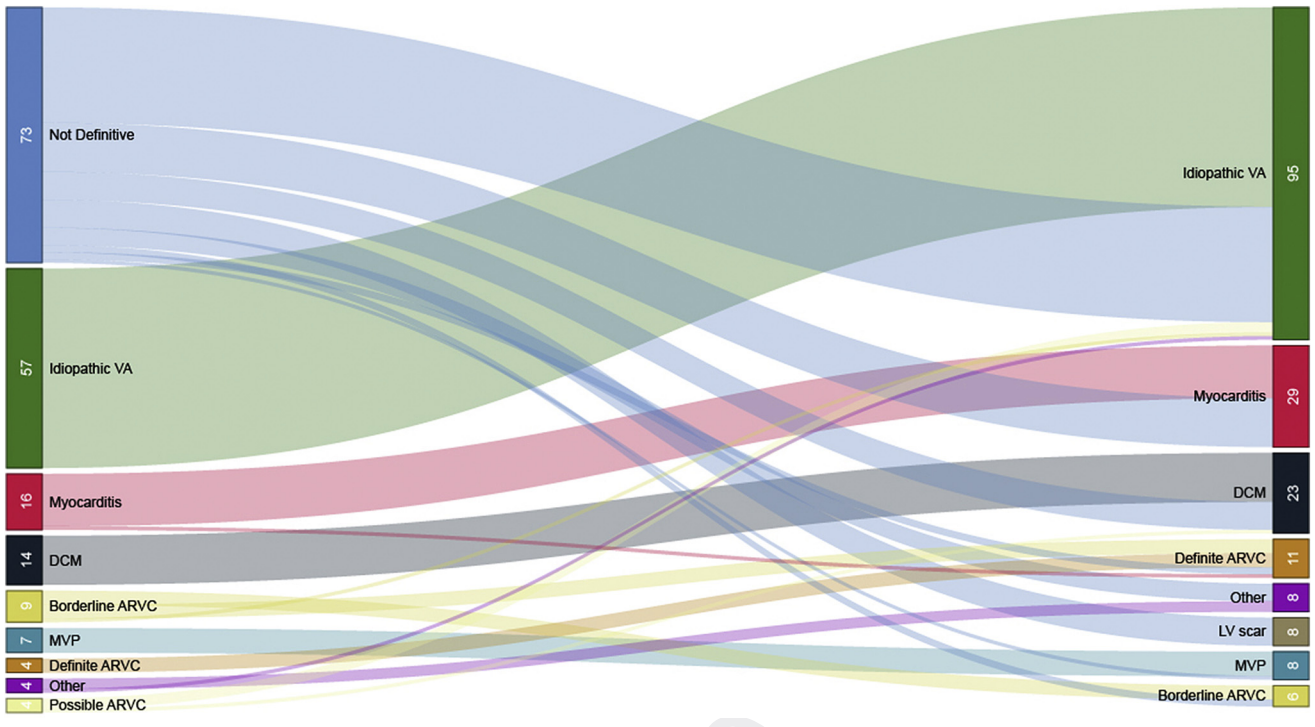

Figure 3 Sankey diagram of the reclassification before and after invasive testing (n = 188). **Left column:** diagnoses based on noninvasive findings, including cardiac magnetic resonance imaging. **Right column:** Final diagnoses after electrophysiological study, electroanatomic mapping, and endomyocardial biopsy (when performed). The "Other" label in the left column includes left ventricular noncompaction (LVNC) (n = 2), bicuspid aortic valve (BAV) (n = 1), and right ventricular hypokinesis (n = 1). The "Other" label in the right column includes Brugada syndrome (n = 2), LVNC (n = 2), hypertrophic cardiomyopathy (n = 1), mitochondrial cardiomyopathy (n = 1), right ventricular scar (n = 1), and BAV (n = 1). Abbreviations as in Figures 1 and 2.

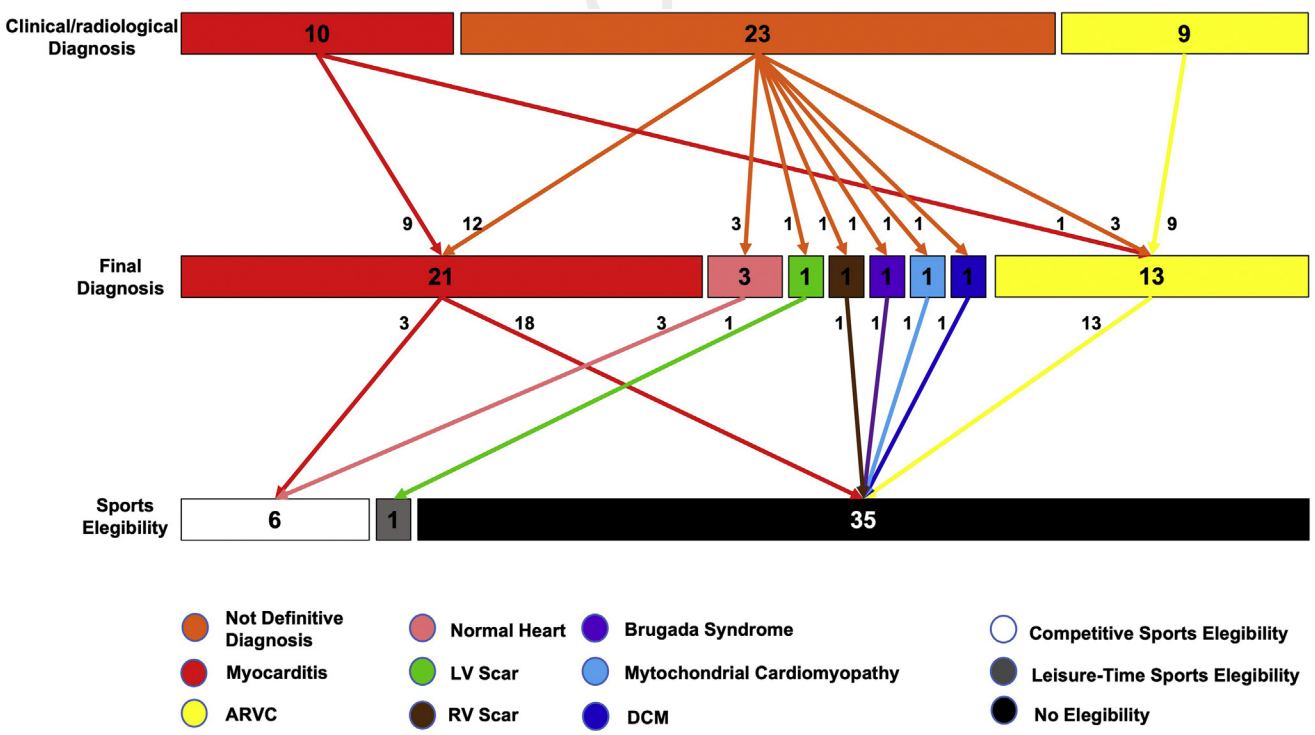

Figure 4 Diagnostic reclassification after endomyocardial biopsy and sports eligibility at follow-up (n=42). Schematic representation of how the diagnosis changed before and after invasive diagnostic tests in the whole cohort of patients undergoing endomyocardial biopsy. **Top bar:** Diagnoses after noninvasive tests. **Middle bar:** Final diagnoses after invasive tests. **Bottom bar:** Sports eligibility at 6-month follow-up. Note that most patients without definitive findings after noninvasive evaluations were reclassified after invasive tests. Abbreviations as in Figures 1 and 2.

Table 3 Univariable and multivariable factors associated with sports ineligibility at 6-month follow-up (n = 179)

	Univariable analysis			Multivariable analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Presence of LGE	**17.37**	**7.88–40.85**	**.00005**	**14.13**	**4.55–50.47**	**.0086** Q7
Presence of abnormal voltage areas by EAM	**9.02**	**4.17–20.50**	**.002**	**5.46**	**1.68–18.92**	**.0055**
History of syncope	**7.30**	**2.07–34.05**	**.004**	**12.92**	**1.44–143.80**	**.028**
Abnormal echocardiogram	**4.24**	**2.10–8.71**	**.044**	**3.35**	**1.14–10.33**	**.030**
Sustained VT/VF induction by EPS	12.56	3.15-83.92	.0015	19.57	1.29–563.71	.054
Exercise stress testing						
VA reduction	4.82	1.27–18.67	.020	5.30	0.71–38.64	.10
Sustained VT induction	7.50	1.41–44.75	.018	0.11	0.0021–6.47	.28
Family history						
Cardiomyopathy	6.78	0.84–139.12	.10	0.83	0.033–38.28	.91
Sudden cardiac death	1.81	0.43–7.14	.39	4.87	0.59–37.39	.12
ECG						
Borderline	2.37	0.88–6.15	.079	1.86	0.38–8.22	.42
Abnormal	5.40	2.44–12.36	.029	1.61	0.47–5.50	.45
Male sex	1.83	0.80–4.61	.17	1.87	0.54–7.07	.33
Type of arrhythmia						
Nonsustained VT	1.25	0.58–2.68	.57	1.07	0.32–3.52	.91
Sustained VT/VF	3.30	1.36–8.22	.009	0.43	0.07–2.34	.34
Age	1.02	1.00–1.05	.11	0.98	0.94–1.02	.29
Abnormal morphology and/or function by cMRI	6.18	2.95–13.85	.0081	0.97confint	0.26–3.50	.97

CI = confidence interval; OR = odds ratio; other abbreviations as in Tables 1 and 2.

according to the performance of invasive tests is shown in Supplemental Figure 5.

After weighing for multiple variables derived from history (age, gender, family history of cardiomyopathy or SCD, personal history of syncope, and type of VA) and noninvasive tests (results of ECG, stress testing, echocardiography, and cMRI), only history of syncope, abnormal echocardiographic findings, and presence of late gadolinium enhancement (LGE) were significantly associated with a lower chance of sports eligibility at 6-month follow-up (Table 3). When adding information derived from invasive assessments to the regression model, presence of abnormal voltage areas by EAM was significantly associated with a significantly lower probability of sports eligibility at follow-up (Table 3). Adding results of invasive tests (EPS and EAM) significantly improved the performance of the regression model for the prediction of sports eligibility at 6-month follow-up over and above noninvasive information [Wald test $P = .0099$; c-statistic of the model incorporating noninvasive variables: 0.88 (95% CI 0.82–0.94); c-statistic of the model incorporating both noninvasive and invasive variables: 0.91 (95% CI 0.86–0.96)] (Figure 5).

Discussion

After recent dramatic reports of sports-related SCDs, the sports eligibility assessment of athletes with VAs has generated consistent uncertainties and preoccupation.

The hypothesis made by some investigators[2] that VAs can be a physiological consequence of physical training in athletes and a feature of the athlete's heart adaptive phenotype should not prevent sports doctors and clinical cardiologists from considering the possibility that the arrhythmias themselves may be due to a potentially malignant underlying myocardial disease.[1,3–5]

Our data suggest several main messages for the clinicians. (1) After noninvasive evaluation including cMRI, some degree of diagnostic uncertainty persisted in more than one-third of athletes with VAs. (2) A comprehensive invasive workup, including EAM, EPS and EAM- or cMRI-guided EMB, could improve diagnostic definition of athletes with VAs. (3) In terms of reclassification, the comprehensive invasive workup had the highest impact in those cases when noninvasive tests did not lead to a definitive diagnosis. (4) Our workup provided important elements for arrhythmic risk stratification and helped in the selection of patients for ICD implantation. (5) Such an extensive assessment proved safe, with few major complications. (6) Information derived from invasive procedures was significantly related to sports eligibility status at follow-up over and above data obtained by history and noninvasive tests.

Clinical importance of diagnostic reclassification and implications for sports eligibility assessment

Currently, there is no consensus on the extent to which investigations should go so that important diagnoses in athletes with VAs are not missed.[4,16–18] Although cMRI is useful for diagnosing myocarditis and ARVC, it is only through characterization of myocardial inflammatory infiltrates and identification of viral genomes in the myocardium that tailored treatments with immunosuppressive and/or antiviral agents can be initiated, with the potential to modify the disease's natural history.[8] Furthermore,

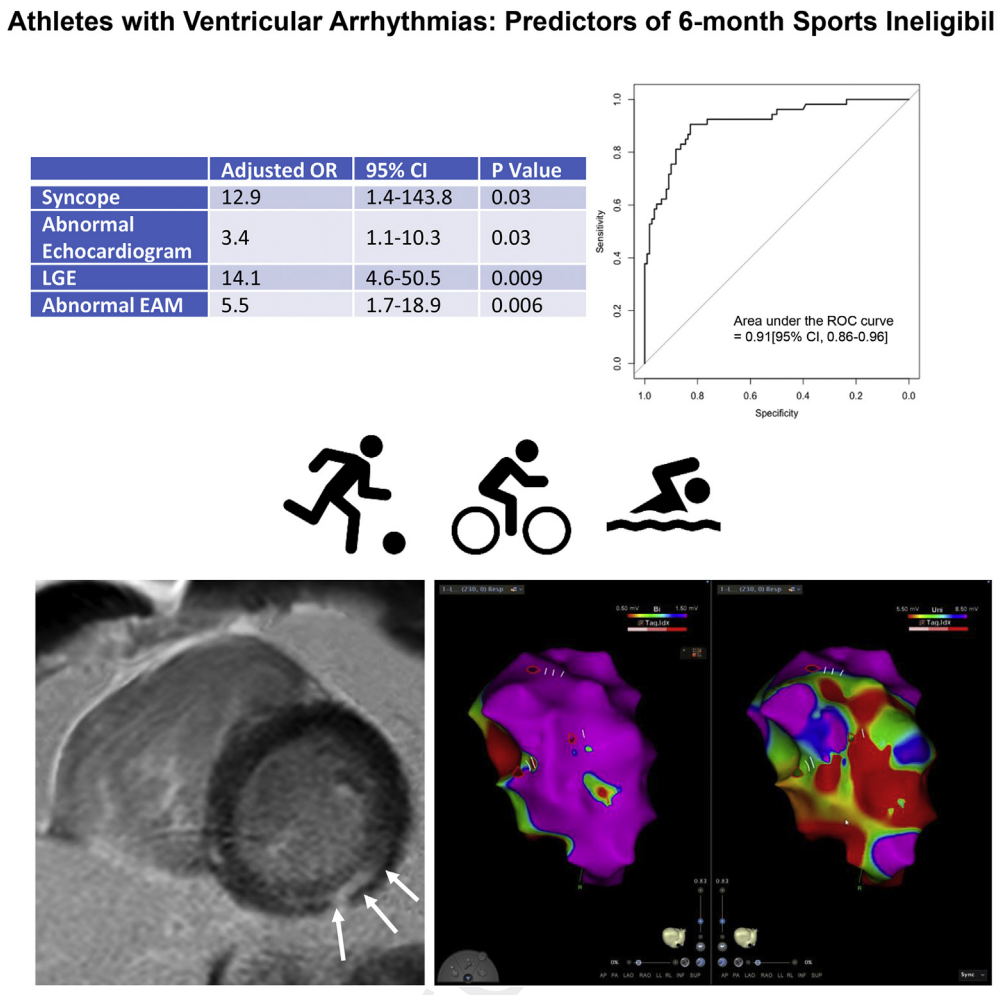

Figure 5 **Top left:** Significant predictors of sports ineligibility at 6-month follow-up among athletes with ventricular arrhythmias. **Top right:** Receiver operating characteristic curve (ROC) of a model for the prediction of 6-month sports ineligibility according to both noninvasive and invasive tests. Note that the diagnostic performance of the model is almost perfect (c-statistic, 0.91). **Bottom left:** Cardiac magnetic resonance imaging, late gadolinium enhancement (LGE) short-axis view showing a hyperintense region with a stria pattern in the inferolateral walls of the left ventricle in a cyclist with premature ventricular complexes. **Bottom right:** Corresponding electroanatomic reconstructions of the left ventricle, on bipolar **(left)** and unipolar **(right)** mapping (posteroanterior projections), showing a large low-voltage area *(red)* in the posterior wall of the left ventricle in the unipolar analysis. The patient underwent endomyocardial biopsy, which revealed a diagnosis of chronic myocarditis. CI = confidence interval; EAM = electroanatomic mapping;

training-induced RV remodeling and RV myocarditis can overlap with ARVC.[14,19–22] Accumulating evidence supports a comprehensive invasive approach in which EAM- or cMRI-guided EMB plays a pivotal role.[3,5,6,23]

Remarkably, all the diagnostic and prognostic benefits of the comprehensive invasive workup were accrued with few excess hazards for the patients, confirming the findings reported by other investigators.[28] The few complications reported (none of them EMB-related) were mostly due to the femoral vascular access; cardiac perforation never occurred. The hazards conferred by invasive diagnostic tests and EMB seem especially justified in competitive athletes, who often strongly desire to return to competitions and, therefore, place a high value on reaching a precise diagnosis, in order to better estimate prognosis and inform specific therapies.[4,12–14,29] Furthermore, our data suggest the existence of a direct relationship between information derived from invasive electrophysiological procedures (EPS and EAM) and sports eligibility status at follow-up, supporting the judicious use of such a thorough approach in athletes motivated to return to play.

However, our data show that there was no diagnostic reclassification when invasive assessments were performed in athletes with normal findings at noninvasive tests, confirming that noninvasive tests can effectively serve as a tool to risk-stratify athletes and select candidates for further exams in a logical way.[17,18,29]

Study limitations

First, a considerable proportion of patients refused their consent for invasive diagnostic tests. Nonetheless, to the best of our knowledge, this is the largest reported cohort of athletes undergoing invasive evaluations, including EAM and EAM- or cMRI-guided EMB. Because we only use 3-lead ECG monitors in our centers, we were unable to provide a

breakdown of the morphology of VAs. Furthermore, the high prevalence of heart disease in our cohort of athletes with complex VAs (45%) likely is influenced by referral bias, whereby athletes with a high suspicion of significant structural heart disease were sent for evaluation to our tertiary centers. Unfortunately, we were not able to collect data on exercise imaging tests and genetic testing. However, coronary artery disease was rare in our cohort, and a family history of SCD or cardiomyopathy was elicited in a minority of cases. Furthermore, results of genetic testing often cannot be obtained earlier than several months after blood sampling, even in tertiary-level centers, which is an exceedingly long delay for athletes who wish to return to play. Finally, cardiologists performing invasive procedures at our centers had considerable experience in EPS, EAM, and EMB; therefore, the reported safety and accuracy of our invasive evaluation possibly cannot be generalized to smaller centers with a lower volume of procedures.

Conclusion

A thorough noninvasive and invasive workup of athletes with complex VAs provided precise diagnostic and prognostic information, significantly increasing the number of diagnoses that could be provided over noninvasive tests. EAM- or cMRI-guided EMB allowed the reclassification of patients with unclear findings after noninvasive evaluation, while carrying a low risk of adverse events. A comprehensive diagnostic workup could improve sports eligibility assessment over and above information obtained throughout medical history and noninvasive tests. Accordingly, VAs should be considered a red flag possibly indicating an underlying concealed cardiomyopathy.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2021.09.013.

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