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REVIEW

Differentiating Athlete's Heart from Cardiomyopathies – The Right Side

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a recognised cause of sudden cardiac death during exercise in young athletes. Competitive exercise is also known to accelerate progression of ARVC and exercise restriction is an important part of disease management. Regular endurance training can induce physiological changes detectable on electrocardiography and imaging which may overlap with pathological findings caused by ARVC, thus making differentiation of athlete's heart from ARVC difficult in some cases. This review will discuss the changes of athlete's heart, particularly as it affects the right ventricle, the diagnostic criteria for ARVC and how diagnostic accuracy is affected in athletes. A practical approach to this clinical problem is outlined.

Keywords Athlete's heart • Cardiomyopathy • Diagnosis • Exercise • Arrhythmogenic right ventricular cardiomyopathy

The Clinical Problem

Sudden cardiac death (SCD) during exercise remains a rare, but devastating occurrence in both young and older athletes. In younger individuals, inherited cardiac conditions which predispose the athlete to lethal arrhythmias are the dominant cause, with the precise breakdown of causes varying by geographic location. This variation probably reflects global variability in genetic make-up. Arrhythmogenic right ventricular cardiomyopathy (ARVC) is the most common cause of SCD in the Veneto region of Italy [1], and individuals with ARVC have a five-fold increase in the risk of SCD with exercise than those who do not exercise [2]. Because SCD may the first manifestation of the underlying disease in an otherwise asymptomatic athlete, Italy has adopted routine screening of all Italian participants in organised sport to identify this, and other inherited diseases likely to lead to SCD, so that those affected can receive treatment and be given appropriate advice regarding sports participation, most commonly exclusion from competitive sport [3]. Accurate diagnosis thus requires reliable differentiation of those with underlying disease from those athletes with the changes of ''athlete's heart''. As with the left heart, there is significant overlap in findings of ARVC and those of an athlete's heart leading to a significant clinical challenge.

In addition, athletes may develop symptoms such as palpitations, dizziness or syncope, which may be early symptoms of underlying cardiac disease, or may have a family member with cardiac disease, leading to investigations such as an electrocardiograph (ECG) or echocardiography. Abnormalities suggestive of right heart disease detected on these investigations require more detailed evaluation to separate pathological from physiological change. Thus the clinician requires an understanding of the physiological changes in the right ventricle (RV) produced by exercise training, the features of pathological right heart disease, in particular, ARVC as reflected on investigation, important differential diagnoses and how to apply accepted diagnostic criteria to reach the correct diagnosis.

Impact of Exercise on RV Structure and Function

In the same way as has been described in the left heart [4], regular exercise training changes the structure and function of the right side of the heart. The intermittent volume and pressure load of exercise results in increased right ventricular mass and cavity size, and some increase in wall thickness [5]. The increase in right ventricular volume affects all parts of the ventricle including the inflow, body and outflow portions

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[6], although some data suggest that the right ventricular outflow tract (RVOT) remodels less than other regions [7]. Because the volume load on the left and right heart are the same during exercise, the degree of left and right ventricular dilation is often similar producing a balanced appearance between left and right sides [8]. In endurance athletes, particularly those with very high training volumes, the dilation of the RV can be quite marked and may produce greater change in the RV than the left ventricle (LV), possibly due to the greater increase in wall stress of the RV with exercise when compared to the LV [9]. Thus an endurance athlete with symptoms which could be consistent with ARVC may have features of right ventricular dilation on imaging studies and a suggestive ECG, thus raising the possibility of this important diagnosis. It is also relevant that the degree of ECG change reflecting RV remodelling such as in incomplete or complete right bundle branch block (RBBB) appears to reflect the extent of RV remodelling such that those athletes with a complete RBBB have larger RV volumes than those with incomplete RBBB (IRBBB) and the smallest RV volumes are seen in those without any form of RBBB [10]. The challenge is to separate those with disease from those with an athlete's heart, particularly in the areas where findings overlap.

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) was initially thought to be a developmental abnormality when the first case series was described in 1982 [11], hence the initial term was arrhythmogenic right ventricular dysplasia. It is known to predominantly affect the right ventricle but can also affect the left ventricle, particularly in advanced cases and with certain specific gene mutations. It is believed to affect 1 in 2000 to 5000 individuals and is more common in males. The underlying disorder is due to mutations in desmosomal proteins—the glue which is involved in cellular adhesion and communication between cardiac myocytes. The most common genes associated with development of ARVC are those encoding plakophilin-2, desmoplakin, desmoglein, desmocollin and plakoglobin [12]. This results in myocyte loss, fatty infiltration and fibrosis of the RV myocardium creating a substrate for ventricular arrhythmias and ventricular dysfunction. Because the arrhythmias arise from the right ventricle, the ventricular premature complexes (VPCs) or ventricular tachycardia (VT) will usually have a left bundle branch block (LBBB) morphology. The right ventricular outflow tract (RVOT), the RV apex and the inflow tract appear to be preferentially involved, although many advanced cases are associated with involvement of the LV.

The disease is progressive and four clinical stages of the disease have been described: latent disease, symptomatic ventricular arrhythmias, right heart failure and biventricular failure. Relevant to cardiologists and sports physicians is that ARVC is a known risk factor for exercise-related syncope or SCD in teenagers or young adults, an event which may be the first manifestation in an otherwise healthy individual. It is also known from animal studies in plakoglobin deficient mice [13], and in human studies [14–16], that exercise training accelerates the progression of the disease so that lifestyle modification with avoidance of intense and competitive exercise is a key part of management. A diagnosis of ARVC has implications for ongoing management of the patient, but is also a trigger for cascade screening of family members. Thus accurate diagnosis in affected individuals is critical to institute appropriate management in those with the disease, but also to avoid unnecessary exclusion of athletes who do not have the disease.

Diagnostic Criteria for ARVC

The traditional method for the diagnosis of ARVC is by use of Task Force criteria (TFC) which were first developed in 1994, and modified in 2010 [17], in an effort to improve diagnostic accuracy. The combination of two major, a major and two minor, or four minor criteria are required for a definite diagnosis (Table 1). Whilst there is often a focus on imaging parameters amongst many cardiologists, the finding of right ventricular enlargement with dysfunction only fulfils one major or one minor criterion. Family history, arrhythmias, ECG abnormalities and, possibly, histological findings remain critical for accurate diagnosis of ARVC.

Unfortunately, due to RV remodelling seen with exercise training, the modified TFC do not perform as well in athletes when compared to non-athletes. One study of healthy Olympic athletes found that 32% had RV enlargement within the range of which would fulfil minor criteria and 4% had positive major criteria [6]. The proportion was even higher with endurance athletes, of whom over 50% met minor criteria and almost 25% met major criteria based on RVOT size. Similarly, Oxborough found that 20% of endurance athletes had RVOT diameters which were greater than the cut-off for major criteria for ARVC [18]. Right ventricular ejection fraction or its echocardiographic surrogate fractional area change (FAC) can be mildly reduced in highly trained endurance athletes as a normal finding, thus further confounding diagnosis. Unfortunately, most studies examining diagnostic performance have compared athletes without ARVC to non-athletes with ARVC, thus amplifying differences between groups, but failing to specifically address the question about differentiating athletes with ARVC from athletes without ARVC. One comprehensive study of patients with ARVC and athletes, with and without T wave inversion (TWI) that may indicate ARVC, found that parameters such as distribution of TWI, RV size, apical RV wall motion abnormalities and RVFAC by echo between 31 and 41%, all of which are contained in the revised Task Force criteria, were poor discriminators between athlete's heart and ARVC [19]. They identified factors which may favour a diagnosis of one versus the other in difficult cases (Table 2) and which may be clinically useful in the population.

Table 1 Summary of modified Task Force Criteria for diagnosis of ARVC. Readers should read the original criteria for more detail [17].

Domain	Major Criteria	Minor Criteria
I. Global or regional dysfunction and structural alterations	***By 2D echo***	***By 2D echo***
	● Regional RV akinesia, dyskinesia or aneurysm and one of the following (end-diastole):	● Regional RV akinesia, dyskinesia or aneurysm and one of the following (end-diastole):
	- PLAX RVOT ≥32 mm (or ≥19 mm/m^2)	- PLAX RVOT ≥29 to <32 mm (or ≥16 to <19 mm/m^2)
	- PSAX RVOT ≥36 mm (or ≥21 mm/m^2)	- PSAX RVOT ≥32 to <36 mm (or ≥ 18 to <21 mm/m^2)
	- or FAC ≤33%	- or FAC >33 to ≤40%
	By MRI	***By MRI***
	● Regional RV akinesia or dyskinesia or dyssynchronous contraction and one of the following:	● Regional RV akinesia or dyskinesia or dyssynchronous contraction and one of the following:
	- Ratio of RV end-diastolic volume to BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female)	- Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m^2 (male) or ≥ 100 mL/m^2 (female)
	- or RV ejection fraction ≤40%	- or RV ejection fraction ≤40 to <45%
	By RV angiography	
	Regional RV akinesia, dyskinesia or aneurysm	
II. Tissue characterisation of wall	● Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy	● Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
III. Repolarisation abnormalities	● Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete right bundle branch block QRS ≥120 ms)	● Inverted T waves in leads V1 and V2 in individuals >14 years of age (in the absence of complete right bundle branch block) or in V4, V5, or V6 ● Inverted T waves in leads V1, V2, V3, and V4 in individuals >14 years of age in the presence of complete right bundle-branch block
IV. Depolarisation/conduction abnormalities	● Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3)	● Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG ● Filtered QRS duration (fQRS) ≥114 ms ● Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms ● Root-mean-square voltage of terminal 40 ms ≤20 μV ● Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R′, in V1, V2 or V3 in the absence of a complete right bundle branch block
V. Arrhythmias	● Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	● Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis ● >500 ventricular extrasystoles per 24 hours (Holter)

Table 1. (continued).

Domain	Major Criteria	Minor Criteria
VI. Family History	● ARVC confirmed in a first-degree relative who meets current Task Force criteria	● History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria
	● ARVC confirmed pathologically at autopsy or surgery in a first-degree relative ● Identification of a pathogenic mutation categorised as associated or probably associated with ARVC in the patient under evaluation	● Premature sudden death (<35 years of age) due to suspected ARVC in a first-degree relative ● ARVC confirmed pathologically or by current Task Force Criteria in second-degree relative

Abbreviations: RV, right ventricle: PLAX, parasternal long axis view; PSAX, parasternal short axis view; RVOT, RV outflow tract; BSA, body surface area; FAC, fractional area change; SAECG, signal averaged electrocardiogram; ARVC, arrhythmogenic right ventricular cardiomyopathy; MRI, magnetic resonance imaging.

Table 2 Findings which may be help discriminate between athlete's heart and ARVC in the presence of anterior T wave inversion and RV enlargement (adapted from Zaidi et al. [19] and Chivulescu et al. [36]).

Consider athlete's heart	Consider ARVC
Balanced biventricular enlargement (RV basal dimension/LVEDD ≤ 0.9 by echo) (RVEDV/LVEDV ≤ 1.2 by CMRI)	Reduced RV systolic function (RVFAC ≤ 30% by echo) (RVEF ≤ 45% by CMRI)
Voltage criteria for LVH or RVH on ECG	RV wall motion abnormalities
Max precordial QRS amplitude >3.3 mV	Isolated enlargement of RVOT
Biphasic TWI	DGE on CMRI
Convex ST elevation with TWI	Max Precordial QRS amplitude <1.8 mV
Absence of symptoms or family history	TWI with isoelectric ST segment
	>1000 VPCs per 24 hours
	Increased VPCs or SBP rise < 20 mmHg on exercise testing

Abbreviations: ARVC, arrhythmogenic right ventricular cardiomyopathy; LVEDD, left ventricular end diastolic diameter; RVEDV, right ventricular end diastolic volume; LVEDV, left ventricular end diastolic volume; TWI,T wave inversion; LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy; DGE, delayed gadolinium myocardial enhancement; VPC, ventricular premature contractions (or complexes); CMRI, cardiac magnetic resonance imaging; RVOT, right ventricular outflow tract.

Other Causes of RV Enlargement

When faced with any individual who has enlargement of the right ventricle (RV) with global or regional dysfunction, it is important to exclude other causes such as atrial septal defect, partial anomalous pulmonary venous drainage, right-sided valvular regurgitation, sarcoidosis, pulmonary hypertension and previous RV infarction (Figure 1). This may require investigations such as transoesophageal echocardiography, cardiac magnetic resonance imaging (CMRI) or cardiac catheterisation.

Exercise-Induced Right Ventricular Cardiomyopathy

A syndrome of exercise-induced right ventricular cardiomyopathy has been observed in endurance athletes, most commonly reported in cyclists, triathletes and rowers [20], athletes whose sport puts both high dynamic and static loads on the cardiovascular system. These athletes develop ventricular arrhythmias originating from the right ventricle, and which are associated with reduced right ventricular function, which may be seen at rest in some athletes or may be seen as reduced right ventricular contractile reserve on exercise testing [21]. This does not appear to be due to the most commonly recognised desmosomal mutations, which cause familial ARVC and these athletes do not have definite ARVC by modified Task Force criteria [14]. Whilst transient RV dysfunction associated with elevations in troponin and B-type natriuretic peptide has been described following ultra-endurance exercise [22–25], most studies report a return to pre-exercise RV function at 1 week post event [26]. It is, therefore, thought that repeated episodes of endurance exercise, both in the form of training and competition result in cumulative myocardial injury which may, in some cases,

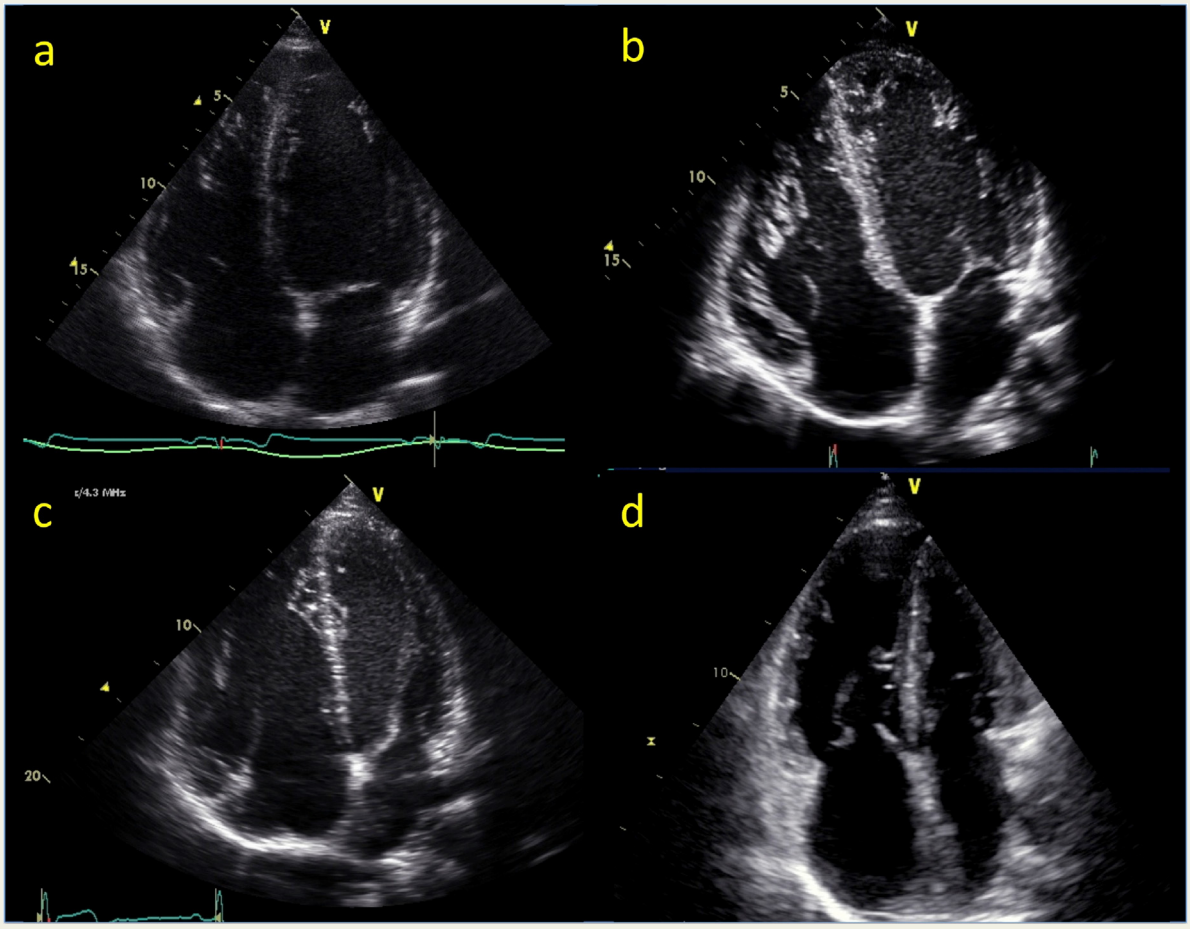

Figure 1 Athletes with RV enlargement of different causes. Panel a: Healthy athlete with balanced enlargement of an athlete's heart, Panel b: Athlete with ARVC with prominent trabeculation and enlargement of the RV more than the LV, Panel c: Athlete with a sinus venosus atrial septal defect and partial anomalous pulmonary venous drainage causing enlargement of the RA and RV. Panel d: Athlete with pulmonary arterial hypertension with a normal sized LV and a dilated RV.
Abbreviations: RV, right ventricular; RA, right atrial; LV, left ventricular; ARVC, arrhythmogenic right ventricular cardiomyopathy.

result in an ARVC-like phenotype (Figure 2) [20]. It is likely that the disproportionate rise in RV wall stress with exercise and the duration of that stress are important haemodynamic factors [9]. It is, however, unclear what other factors predispose some athletes to this condition, although it is possible that they have an as yet unrecognised genetic predisposition which is only expressed phenotypically in the setting of extreme exercise.

ECG Findings

The classical ECG findings of ARVC include the presence of epsilon waves (reproducible low amplitude signals between the end of the QRS and the onset of the T wave), and TWI in the precordial leads beyond lead V2. In sedentary Caucasian populations, the appearance of TWI beyond lead V2 is rare in normal individuals [27]. In an athletic population, this is not so simple. Athletes of Afro-Caribbean descent may have TWI extending to lead V4 and preceded by ST segment elevation as a normal finding [28]. Endurance athletes, particularly elite endurance athletes, have a higher rate of TWI beyond V2 than both healthy control subjects [29] and non-endurance athletes [30]. The most likely mechanism is lateral displacement of the apex due to cardiac enlargement into the left chest [29]. Whilst epsilon waves are likely to be highly specific, a study by Zaidi et al. comparing a cohort of 35 patients with ARVC to 80 athletes with and without TWI did not identify any subjects with epsilon waves, suggesting the sensitivity is low in clinical practice [19]. Thus, endurance athletes may have false positive findings based on the distribution of anterior TWI.

Echocardiography

Evaluation of the right heart by echocardiography provides variables which form part of the TFC. It is recommended that

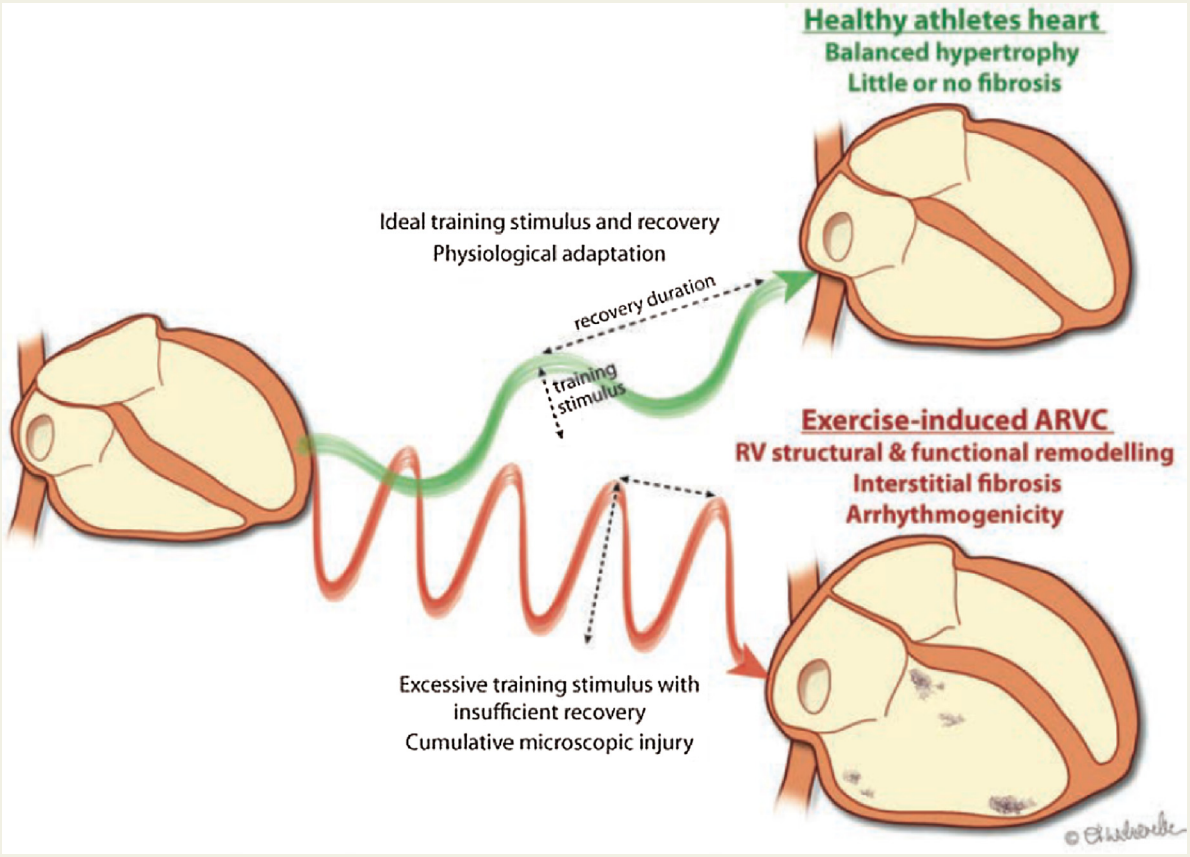

Figure 2 Proposed mechanism of exercise-induced right ventricular cardiomyopathy Repeated episodes of excessive training and insufficient recovery may cause cumulative fibrosis within the right ventricle (Reproduced from Heidbuchel et al. [20] with permission © 2012).

an RV-focussed apical view is used in addition to standard apical views to allow better visualisation of the RV free wall and make quantification of parameters such as RV fractional area change (FAC) easier [31]. Quantitative assessment of the right ventricular outflow tract (RVOT) dimensions in the parasternal long and short axis views should be undertaken. Right ventricular FAC should be measured from the apical four-chamber view or an RV-focussed apical view (Figure 3). There are published guidelines for accurate and reproducible measurement of these parameters [32]. Careful attention to how views are obtained and awareness of issues such as tethering of the RV free wall by the moderator band, which may produce the appearance of segmental RV wall motion abnormalities (Figure 4), are important to avoid an incorrect diagnosis.

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMRI) provides the ability to image the whole heart at high spatial resolution and has become the gold standard for evaluation of cardiac chamber volume, and thus provides the most accurate measures of right and left ventricular ejection fraction. Right ventricular volumes and ejection fraction contribute major or minor imaging criteria for a diagnosis of ARVC. CMRI is also the most accurate means by which to determine whether RV and LV enlargement are balanced in an athlete using calculated LV and RV volumes. Whilst CMRI can assist with diagnosis, it can also be a source of misdiagnosis [33]. The ability of CMRI to identify regions of myocardial scarring with delayed enhancement following gadolinium administration or myocardial fat infiltration sounds an attractive means of identifying cases of ARVC, but this is not part of the diagnostic criteria and is technically very challenging due to the thin walled RV. Abnormalities of the RV wall were the major source of misdiagnosis documented previously [33]. Because of this, the key parameters by which CMRI can help to differentiate ARVC from athlete's heart are the presence of regional wall motion abnormalities and reduced RV ejection fraction, but not increased RV volumes [34].

Exercise Testing

Provocative testing with exercise may have a role in the identification of ARVC or other forms of RV dysfunction

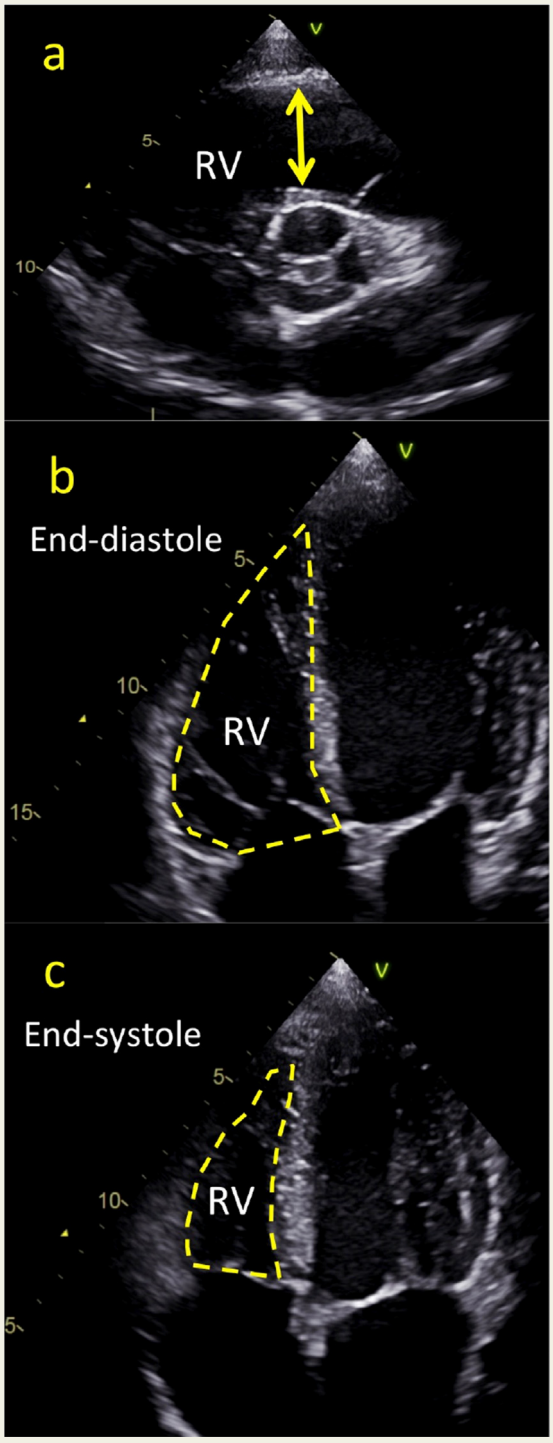

Figure 3 Measurement of RVOT dimension in the parasternal SAX view (panel a) and RV area at end-diastole (panel b) and end-systole (panel c). RV FAC is calculated as ((RV area end-diastole – RV area end-systole)/RV area-end-diastole) x 100.
Abbreviations: RVO, right ventricular outflow tract; SAX, short axis view; RV, right ventricular; FAC, fractional area change.

in an athlete. Detection of VT with a LBBB morphology during exercise testing may provide major or minor criteria for ARVC, depending on the axis of the arrhythmia [17]. Exercise testing with imaging by CMRI or echo to measure RV contractile reserve may be useful for early identification of right ventricular pathology, although this has not been specifically assessed at a diagnostic level in possible ARVC. It has been shown in athletes with VT arising from the RV, some of whom may have ARVC and some may have exercised-induced ARVC, that there is often a failure to augment RV contraction with exercise despite normal resting RV function. Failure to augment RV function was an accurate way to differentiate those with arrhythmias from those without arrhythmias [21], and this methodology shows promise for differentiating athlete's heart from ARVC and like syndromes. The results have been similar using either CMRI or echocardiography as the imaging modality. Whilst its accuracy has yet to be specifically tested, right ventricular stress testing for normal augmentation may prove a useful diagnostic strategy in the future.

A Practical Approach for the Clinician

When differentiating athlete's heart from ARVC, the first question to be considered is whether the individual is exercising enough to induce the changes of the athlete's heart. Generally more than 3 hours of sports activity per week is required to begin to see changes of athlete's heart [35] and greater levels of activity are associated with more marked changes. Thus, in someone doing 3 or less hours per week of exercise, observed changes in RV structure and function should not be attributed to exercise.

Cardiac electrical activity should be evaluated with 12-lead ECG, exercise ECG and Holter monitor looking at whether major or minor criteria for ARVC are present. Once again, the reduced specificity of anterior T wave inversion on a resting ECG in endurance athletes and black athletes should be considered.

Cardiac structure and function should be evaluated by echo or CMRI if this has not already been done to see if structural or functional criteria for ARVC are met, bearing in mind the possible pitfalls discussed above in endurance athletes. In asymptomatic athletes with no family history of ARVC, the presence of anterior TWI and a balanced pattern of ventricular enlargement, even if the measures of RV enlargement are within the range that form part of the Taskforce Criteria, are most likely to be benign [19]. Again, the degree of RV enlargement should also be in proportion to the amount of exercise the athlete is undertaking such that severe enlargement should not be seen in a recreational athlete performing 4 hours of exercise per week, but would not be unusual in a professional endurance athlete undertaking 20 hours of training and competition per week.

A family history of ARVC or unexplained SCD should be sought and results from autopsy and genetic testing sought if

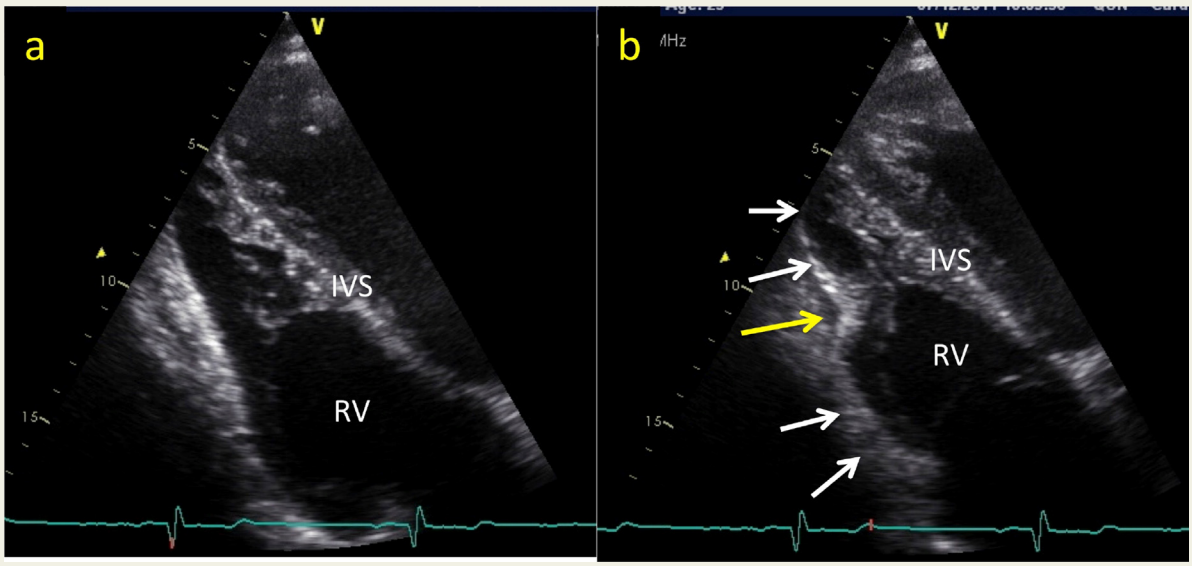

Figure 4 Focussed right ventricular (RV) view of the right ventricle in a healthy endurance athlete in end-diastole (panel a) and end-systole (panel b). Tethering of the RV free wall by the moderator band (yellow arrow) produces the appearance of apical and basal wall motion abnormalities which may lead to a false positive diagnosis of ARVC.
Abbreviations: RV, right ventricular; ARVC, arrhythmogenic right ventricular cardiomyopathy

they are available. A confirmed diagnosis in a first-degree relative or the presence of mutation recognised to cause ARVC provide a major criterion for diagnosis of ARVC.

When in doubt, consultation with an electrophysiologist, a sports cardiologist and a clinical geneticist can be invaluable in more difficult cases, as there are significant implications of both a false positive or a false negative diagnosis. It is possible that other provocative testing as that described above, assessing RV contractile reserve [21], may be useful in the future either for diagnosis or risk stratification. In cases which remain unclear and no definite diagnosis of ARVC is reached, despite an extensive evaluation, the athlete should be allowed to continue to exercise, but should have ongoing follow-up and surveillance, as further change with development of definite phenotypic expression can happen over time.

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