Highly trained athletes Athlete's heart adaptations versus Arrhythmogenic Cardiomyopathy

ACM: ***this is the newest and appropriate designation (not universally accepted yet)***
Denominations: arrhythmogenic cardiomyopathy (ACM); ARVC: arrhythmogenic right ventricular cardiomyopathy (unfortunately this is the most used term currently); arrhythmogenic right ventricular dysplasia (ARVD); ARVC/dysplasia (ARVC/D); Left-dominant arrhythmogenic cardiomyopathy (LDAC); and Arrhythmogenic LV cardiomyopathy (ALVC).

Regular intensive physical activity is associated with no pathological changes in cardiac morphology referred to as "athlete's heart". Nonetheless, in the athletic population, the presence of RV and atrial adaptations, in particular dilatation, is described and has to be considered in the differential diagnosis with ACM which is an important cause of SCD in young athletes. Bauce et al data suggest that athlete's heart can be differentiated from ACM through an accurate clinical and instrumental non-invasive evaluation protocol including ECG, SAECG and TTE. ECG findings suggestive of ACM include the presence of a negative TWI beyond V1 in the precordial leads, incomplete RBBB and low QRS voltage. Both athletes and ACM patients demonstrate RVH compared with controls; however, RV cavity size is not significantly larger in ACM patients than in athletes. On the contrary, ACM is significantly larger in ACM subjects compared with athletes. Furthermore, all ACM patients show localized RV kinetic alterations, an abnormality not detected in athletes and controls (**Bauce B, *et al.* Differences and similarities between arrhythmogenic right ventricular cardiomyopathy and athlete's heart adaptations. Br J Sports Med. 2010;44:148-54. doi: 10.1136/bjsm.2007.042853**).
Physical exercise has been identified as a strong determinant of phenotypic expression of the ACM, arrhythmia risk, and disease progression. Current guidelines advise that individuals with ACM should not participate in competitive or frequent high-intensity endurance exercise. Exercise-induced electrical and morphological para-physiological remodelling (the so-called 'athlete's heart') may mimic several of the classic features of ACM. Therefore, the current International Task Force Criteria for disease diagnosis may not perform as well in athletes. Clear adjudication between the two conditions is often a real challenge, with false positives, that may lead to unnecessary treatments, and false negatives, which may leave patients unprotected, both of which are equally inacceptable.

Similitudes and divergences between ACM and Athlete heart (Table 1 and Figure 1)

Table 1

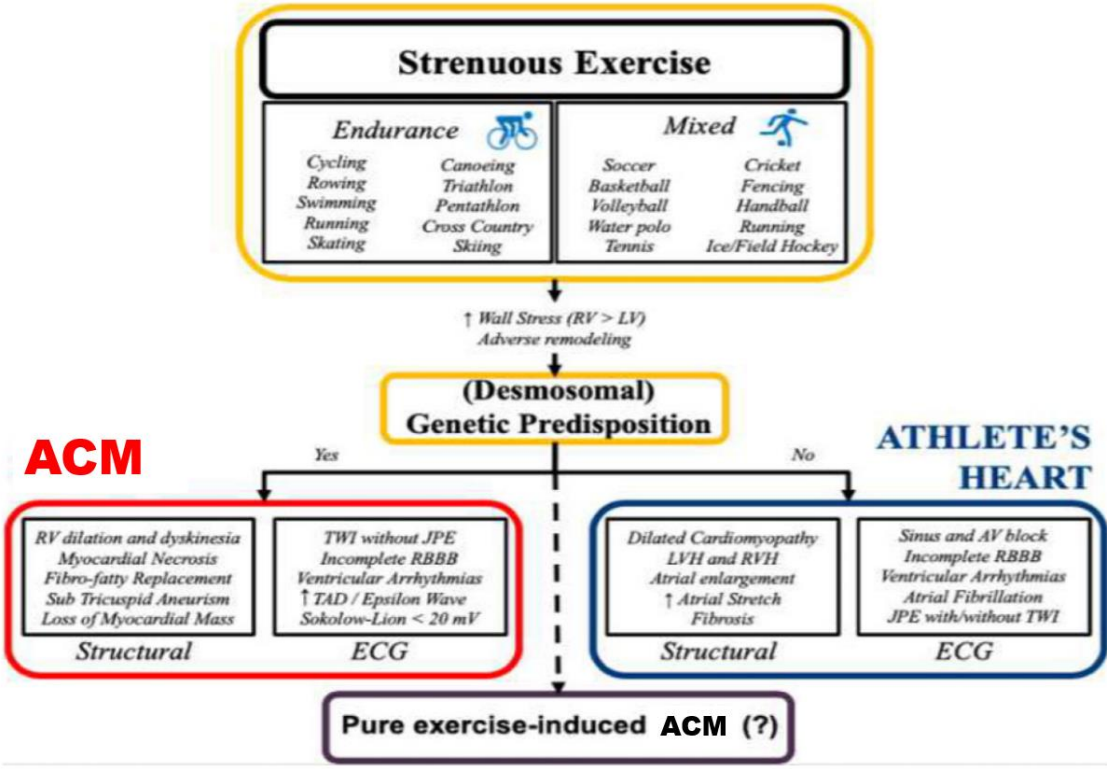
ACM Structural/image	Athlete heart Structural/image
RV dilatation akinesia and dyskinesia: Wall motion abnormalities; Myocardial necrosis; Fibro-fatty replacement; Loss of myocardial mass, LGE (late gadolinium enhancement); Macroscopically detectable changes, both at CMRI and/or EMB (1).	Dilated Cardiomyopathy, Atrial Enlargement, Atrial Stretch augmentation, LVH, RVH without akinesia, Fibrosis. No fibro-fatty replacement.
ACM ECG alterations 80% (2;3) No J-point elevation, extensive TWI IRBBB, CRBBB(RBBB are not frequent in early stages, but its overall reported prevalence is not low and may increase over time.(4), TAD (Terminal Activation Duration), Epsilon wave, Positive Sokolow-Lyon criteria.	Athlete heart ECG alterations, Sinus and AV block, IRBBB, Ventricular arrhythmias, AF, J-point elevation followed by TWI. Positive Sokolow-Lyon criteria.
Exercise stress test BNP and pro-BNP correlate with the extension of LV involvement (5)	Exercise stress test Increases in levels of circulating cardiac biomarkers: troponin T, D-dimer, B-type natriuretic peptide (BNP), and N-terminal pro-BNP after physical exercise
Trans-thoracic Echo (TTE) TTE often is the first-line imaging modality in a patient with suspected ACM because of its widespread availability and low cost. TTE provides structural and functional information on all cardiac chambers, although visualization of the RV requires special emphasis and expertise. In addition, in	Trans-thoracic Echo (TTE) Increased RV mass and cavity size, alongside with an increase in wall thickness and reduction in global systolic function (7). Up to 81% of athletes show a round-shaped apex, and both prominent RV trabeculations and hyperreflective moderator bands have been reported in healthy athletes (8). Due to this

patients with an ICD, TTE may be used for serial evaluation to evaluate disease progression. CMR has high spatial resolution and a theoretically unlimited field of view, thereby allowing for detailed visualization of RV wall motion abnormalities. In addition, the 3-dimensional (3D) depiction of anatomy by CMR enables accurate measurement of RV volumes and function. (6)	remodelling, isolated RV measurements at echocardiography do not seem to be useful in differentiating physiologic from pathologic RV dilation. D'Ascenzi et al (9) reported that 41% and 16% of healthy Olympic athletes in their case series presented an RVH within range of minor and major criteria for ACM, respectively. These numbers increased to 50% and 25%, respectively, in a sub-analysis of the same cohort considering endurance athletes only. Oxborough et al reported in a 102 athlete cohort, with 28% of endurance athletes presenting RVOT diameters greater than the ACM major criteria cut-off values (10). Zaidi et al. demonstrated apical RV motion abnormalities at TTE and RV fractional area change between 31% and 40%, both contained in the ITFC, to be poor discriminators for ACM among athletes (11).
Family history Unexplained SCD in family	Family history First in family proband
Irreversible Stop competitive sport eligibility	Reversible (12;13). competitive sport eligibility
Necessary screening family members using a genetic panel comprising of at least all desmosomal genes: DSP (125647), PKP2 (602861), DSC2 (125645), or DSG2 (125671) (14)	Negative genetic testing cannot rule out the disease.
EMB Fibro-fatty replacement is the hallmark of AMC. Low sensitivity and specificity. Risk complications,	EMB
Voltage map guided EMBs: promising results(**15;16;17**)	As a 'rule-out' test have been published, with overall good results **18;19**)

1) **Kirchhof P, et al. Ageand training-dependent development of arrhythmogenic right ventricular cardiomyopathy in heterozygous plakoglobin-deficient mice. Circulation 2006;114: 1799–1806**
2) **Steriotis AK et al., Electrocardiographic pattern in arrhythmogenic right ventricular cardiomyopathy. Am J Cardiol 2009; 103:1302–1308. 65.**

3) **Finocchiaro G, et al. Electrocardiographic differentiation between 'benign T-wave inversion' and arrhythmogenic right ventricular cardiomyopathy. Europace 2019;21: 332–338.**
4) **Jain R, et al. Electrocardiographic features of arrhythmogenic right ventricular dysplasia. Circulation 2009; 120:477–487**.
5) **Akdis D, et al. Predictors of left ventricular involvement in arrhythmogenic right ventricular cardiomyopathy. Am Heart J 2020; 223:34–43.**
6) **Anneline S J M Te Riele et al. Noninvasive Multimodality Imaging in ARVD/CJACC Cardiovasc Imaging . 2015 May;8(5):597-611. doi: 10.1016/j.jcmg.2015.02.007**
7) **D'Andrea A, et al. Right heart structural and functional remodeling in athletes. Echocardiography 2015;32: S11–22**
8) **D'Ascenzi F, et al. RV remodeling in olympic athletes. JACC Cardiovasc Imaging 2017; 10:385–393**
9) **D'Ascenzi F, et al. RV remodeling in olympic athletes. JACC Cardiovasc Imaging 2017; 10:385–393**
10) **Oxborough D, et al. The right ventricle of the endurance athlete: the relationship between morphology and deformation. J Am Soc Echocardiogr 2012;25: 263–271**
11) **Zaidi A, et al. Clinical differentiation between physiological remodeling and arrhythmogenic right ventricular cardiomyopathy in athletes with marked electrocardiographic repolarization anomalies. J Am Coll Cardiol 2015;65:2702–2711**
12) **D'Ascenzi F, et al. Right ventricular remodelling induced by exercise training in competitive athletes. Eur Heart J Cardiovasc Imaging 2016;17: 301–307.**
13) **D'Ascenzi F, et al. Training-induced right ventricular remodelling in preadolescent endurance athletes: the athlete's heart in children. Int J Cardiol 2017; 236:270–275**.
14) **James CA, et al. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. *J Am Coll Cardiol*. 2013October;62(14):1290–1297.**
15) **Casella M, et al. Feasibility of combined unipolar and bipolar voltage maps to improve sensitivity of endomyocardial biopsy. Circ Arrhythm Electrophysiol 2015;8: 625–632. 107.**
16) **Seizer P, et al J. Left ventricular site-directed biopsy guided by left ventricular voltage mapping: a proof of principle. Int J Cardiol 2013; 168:3113–3114. 108.**
17) **Casella M, et al. Diagnostic yield of electroanatomic voltage mapping in guiding endomyocardial biopsies. Circulation 2020; 142:1249–1260Dello Russo A, et al . Concealed cardiomyopathies in competitive athletes with ventricular arrhythmias and an apparently normal heart: role of cardiac electroanatomical mapping and biopsy. Heart Rhythm 2011; 8:1915–1922.**
18) **Dello Russo A, et al. Concealed cardiomyopathies in competitive athletes with ventricular arrhythmias and an apparently normal heart: role of cardiac electroanatomical mapping and biopsy. Heart Rhythm 2011; 8:1915–1922.**
19) **Narducci ML, et al. Role of extensive diagnostic workup in young athletes and nonathletes with complex ventricular arrhythmias. Heart Rhythm 2020;17: 230–237**

Figure 1 illustrates similitudes and divergences between ACM and Athlete's heart.



The modifications induced by strenuous exercise lead to the development of structural and electrical ACM phenotype (Red Box) upon the presence of an underlying genetic predisposition, while inducing the clinical characteristics of the athlete's heart in the general population (Blue Box). The possibility of developing a pure exercise-induced ACM (Purple Box) upon massive exposure to strenuous exercise in the absence of genetic predisposition has been postulated but its existence is still debated (Dashed line). AV, atrio-ventricular; JPE, J-point elevation; LV, left ventricle; LVH, left ventricular hypertrophy; RBBB, right bundle branch block; RV, right ventricle; RVH, right ventricular hypertrophy; TAD, terminal activation duration; TWI, T-wave inversion. **(Gasperetti A, James CA, Cerrone M, Delmar M, Calkins H, Duru F. Arrhythmogenic right ventricular cardiomyopathy and sports activity: from molecular pathways in diseased hearts to new insights into the athletic heart mimicry. Eur Heart J. 2021 Mar 31;42(13):1231-1243. doi: 10.1093/eurheartj/ehaa821.)**

Table 2 shows other differences between athlete's heart and ACM.

Table 2	Athlete's heart adaptations (highly trained athletes)	ACM

QRS duration	Normal	Prolonged
Low QRS voltages	Very rare	Suggestive
Conduction delay	High incidence	Infrequent
TWI beyond V2	Rare	Suggestive
Normal ECG	97%	38%
QRS voltages	Higher: myocardial hypertrophy	Normal or lower: progressive myocardial atrophy
Ventricular arrhythmias	5%	70%
The ratio between LV and RV end-diastolic volumes	Similar	Significantly smaller
RVOT diameter	Smaller	Significantly larger
RV kinetic alterations,	No	Yes: Localized RV kinetic alterations
RV cavity size	Is not significantly smaller	Is not significantly larger
Moderator band	Normal	Thickened and/or high reflective