

REVIEW

Multimodality imaging in arrhythmogenic cardiomyopathy

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Abstract: Arrhythmogenic cardiomyopathy, as it has been recently redefined, is characterized by progressive myocyte loss with fibrosis and fat infiltration of the myocardium, which finally leads to a broad clinical spectrum ranging from heart failure symptoms to sudden cardiac death. The diagnosis of arrhythmogenic cardiomyopathy is challenging particularly because of its heterogeneity in presentation, which varies from focal right ventricular involvement to biventricular or prominent left ventricular phenotype. In the past decades, the development of new electrocardiographic and imaging diagnostic criteria for arrhythmogenic cardiomyopathy constituted an important area of research and resulted in the elaboration of the Padua criteria. However, even with the widespread availability of modern imaging techniques, there is still a lack of awareness in the health care community and this pathology persists in being under- or misdiagnosed. Given the limited indication of endomyocardial biopsy for the diagnosis of arrhythmogenic cardiomyopathy, one can conclude that the progress that has been made in the last few years in the multimodality imaging field is of utmost importance for the early detection and proper treatment of patients with arrhythmogenic cardiomyopathy, providing valuable prognostic information.

Keywords: multimodality imaging, arrhythmogenic cardiomyopathy, sudden cardiac death.

Rezumat: Cardiomiopatia aritmogenă este caracterizată de pierderea progresivă a miocitelor, însoțită de infiltrarea grăsoasă a miocardului și fibroză, toate acestea conducând în final la un spectru larg de manifestări clinice, de la fenomene de insuficiență cardiacă și până la moarte subită cardiacă. Diagnosticul cardiomiopatiei aritmogene reprezintă adesea o provocare, fapt datorat variabilității fenotipice, aceasta putându-se manifesta fie prin afectarea izolată a ventriculului drept, fie prin afectare biventriculară sau fenotip ventricular stâng dominant. În ultimele decenii dezvoltarea unor criterii noi de diagnostic, atât electrocardiografice, cât și imagistice au constituit un subiect important de cercetare și au condus în final la elaborarea criteriilor Padua. Cu toate acestea, asistăm încă la o subdiagnosticare a acestei patologii. Luând în considerare rolul limitat al biopsiei endomiocardice în diagnosticul cardiomiopatiei aritmogene, se poate concluziona că progresul făcut în ultimii ani în domeniul imagisticii multi-modale este de o deosebită importanță atât pentru diagnosticul precoce, cât și pentru tratamentul adecvat și stratificarea prognostică a acestor pacienți.

Cuvinte cheie: imagistică multi-modală, cardiomiopatie aritmogenă, moarte cardiacă subită.

Arrhythmogenic cardiomyopathy (ACM), as it has been recently redefined¹, is characterized by progressive myocyte loss with fibrosis and fat infiltration of the myocardium, which finally leads to a broad clinical spectrum ranging from heart failure symptoms to sudden cardiac death (SCD). The fibro-fatty infiltration begins from the epicardial layer and progresses to the endocardium². From a historical point of view, the disease was initially considered a dysplasia, secondary to a congenital defect in the formation of the right ventricular myocardium. Subsequently, it has been discovered that the pathological substrate is represented

by a genetic defect in the cardiac desmosomes³. SCD is the first symptom of the disease in up to 20% of cases⁴ and ventricular arrhythmias can appear early in the disease^{5,6}, all these making the immediate diagnosis crucial. The estimated prevalence of ACM ranges between 1:2000 and 1:5000 persons³.

In the past decades, the development of new electrocardiographic and imaging diagnostic criteria for ACM constituted an important area of research and resulted in the elaboration of the Padua criteria. The novelty of these criteria, when compared to the 2010 International Task Force ones, mainly resides in the

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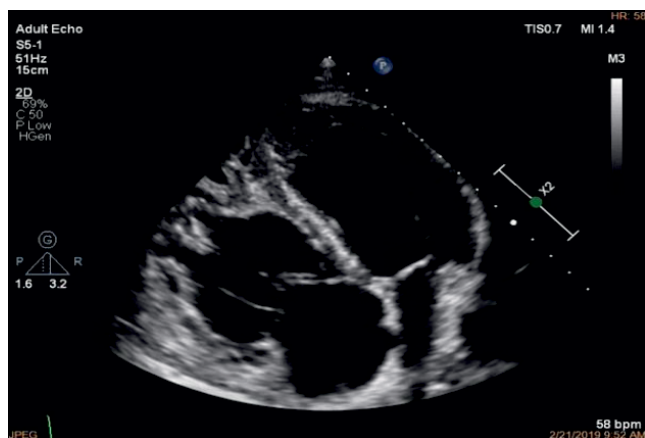


Figure 1. Transthoracic echocardiography, apical 4-chamber view: RV bulging with dilatation; Trabeculations of the LV apex.

addition of the left ventricular phenotype's diagnostic features. The framework designed by Corrado et al. comprises morpho-functional ventricular abnormalities as assessed by echocardiography, cardiac magnetic resonance (CMR) imaging or angiography; tissue characterization findings by CMR; repolarization, and depolarization abnormalities on the ECG; ventricular arrhythmias, and family history/ genetics¹.

Echocardiography plays an important role in both the diagnosis and the identification of patients at high risk. Echocardiographic features are involved in the diagnosis of ACM both as major and minor criteria. The Padua criteria now include only one major echocardiographic criterion for right ventricular involvement, which is represented by the association of right ventricle (RV) akinesia, dyskinesia, or bulging with each of RV dilatation or dysfunction, disregarding their severity (Figure 1). An additional new minor criterion is represented by regional RV wall motion abnormaliti-

es, without RV enlargement or systolic dysfunction. The use of reference values for cavity size and systolic function according to the currently acknowledged nomograms is recommended for better diagnostic accuracy. Reference values also play an important role in the differential diagnosis of physiologic versus pathologic RV enlargement in athletes¹.

Different studies have discussed the optimal echocardiographic views and techniques for best measuring RV dimensions (Figure 2). For example, in 38 patients with ACM and 10 healthy controls, the right ventricular outflow tract (RVOT) diameter measured by the parasternal long axis M-mode of the left ventricle (LV) was best correlated with CMR data⁷. Furthermore, 3D echocardiography is superior to standard 2D echocardiography in measuring RV volumes and the results are generally correlated with those measured by CMR. Moreover, 3D echocardiography is useful in the calculation of RV ejection fraction (EF)⁸.

While in the beginning it was considered that ACM only affects the RV, more and more studies have shown that the LV is also involved^{1,9}. In recent studies, left ventricular involvement was found in 47-60% of cases¹⁰⁻¹². Reduced LV EF, reduced LV global longitudinal strain independent of LV enlargement, as well as regional hypokinesia or akinesia with preserved LV EF, are minor diagnostic criteria for the „biventricular” or „dominant-left” disease variants¹.

Several echocardiographic parameters also have prognostic value and help in identifying patients at high risk for adverse events. Right atrium (RA) area, left atrium (LA) area and volume index, RVOT, RV fractional area change, tricuspid annular plane systolic excursion (TAPSE) and tricuspid annular plane peak systolic velocity were significantly higher in patients with ACM

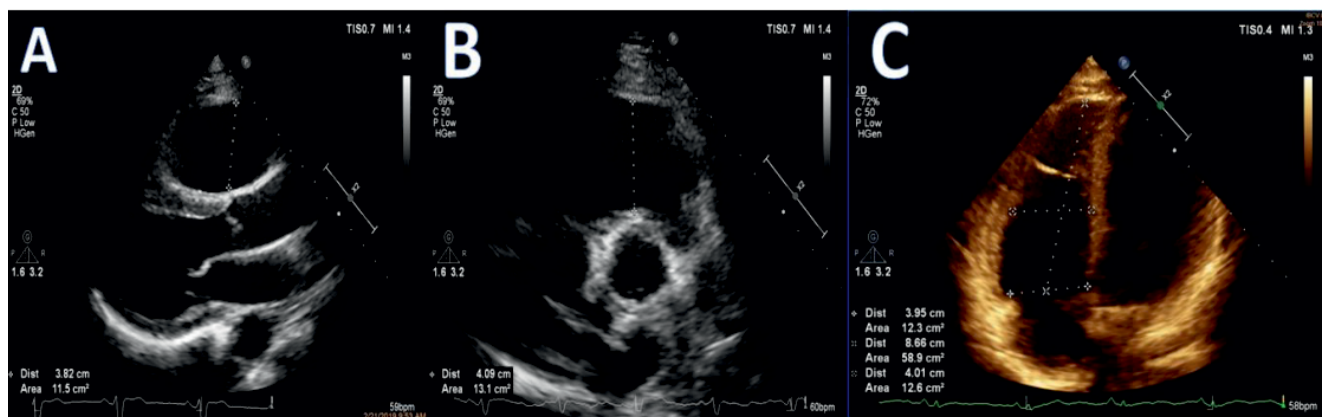


Figure 2. Transthoracic echocardiography- examples of measuring the RV dimensions from different views in a 18y old patient with ACM: A- PLAX, proximal RVOT; B- PSAX, proximal RVOT; C- AP4C, RV basal, mid-cavity and longitudinal dimensions.

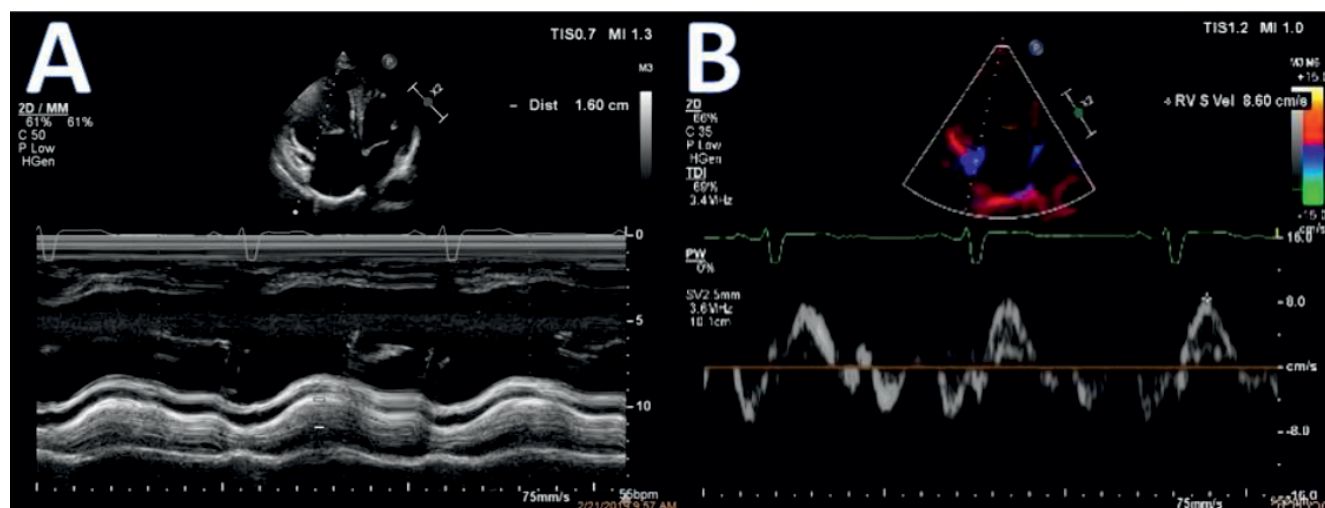


Figure 3. Transthoracic echocardiography- examples of evaluating the longitudinal function of the RV in 49y old patient with ACM: **A.** TAPSE=16 mm; **B.** Tricuspid annular plane peak systolic velocity=8.6 cm/s.

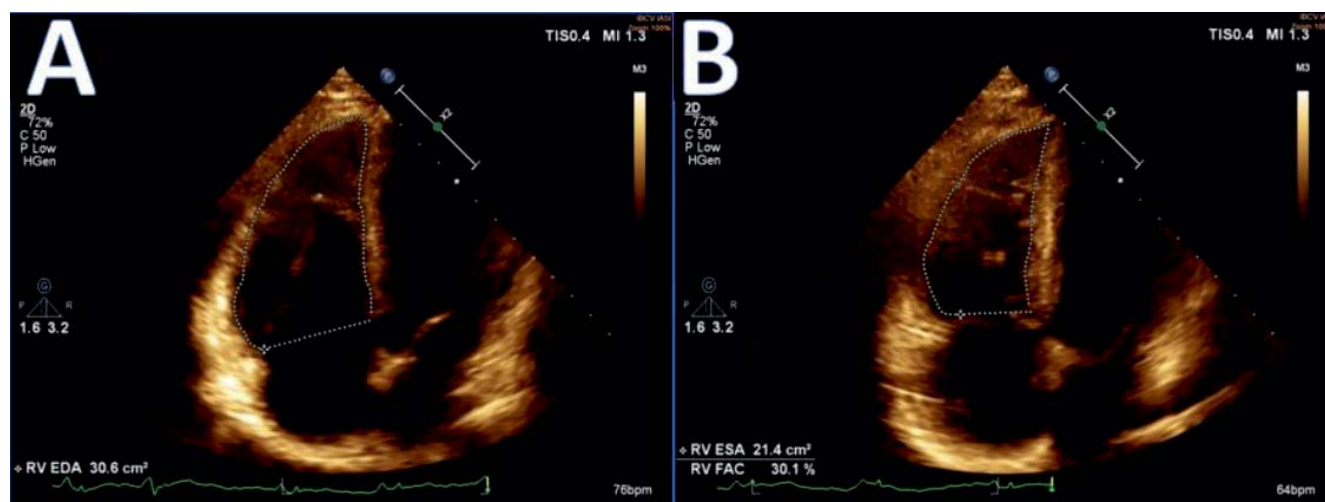


Figure 4. Transthoracic echocardiography- example of RV fractional area change in a 18y old patient with ACM: **A.** End-diastolic area tracing; **B.** end-systolic area tracing; RV FAC 30.1%.

and atrial arrhythmias compared to those without atrial arrhythmias (Figures 3 and 4). RA area, LA volume index, RVOT diameter and TAPSE were associated with increased odds of having atrial arrhythmias, even after adjusting for age¹³. In 48 patients with ACM followed for 6-18 months, e' of the tricuspid valve annulus, peak E velocity of the mitral valve, septal e' at the mitral valve, RA area and volume, alongside with right ventricular myocardial performance index were strong predictors for major adverse cardiac events¹⁴. Moreover, among 64 patients with ACM defined by imaging criteria (echocardiography and CMR), as well as genetic testing, lower RV EF and LV EF values were predictive for biventricular involvement. Moreover,

patients with biventricular involvement had more frequently non-desmosomal mutations, higher levels of hs-cTnT and NT-pro-BNP and shared a history of competitive sports¹⁵.

Speckle tracking imaging is a useful tool for detecting the presence of myocardial fibrofatty tissue which is a well-known marker of contractile dysfunction. In a study that included 34 patients with ACM (17 with previous sudden death or ventricular tachycardia), the right ventricular free wall global longitudinal strain (GLS) and strain rate had significantly lower values in patients with symptoms, when compared with asymptomatic patients. Moreover, a cut-off value of 17.3% for the RV GLS and 1.35 per second for the RV global

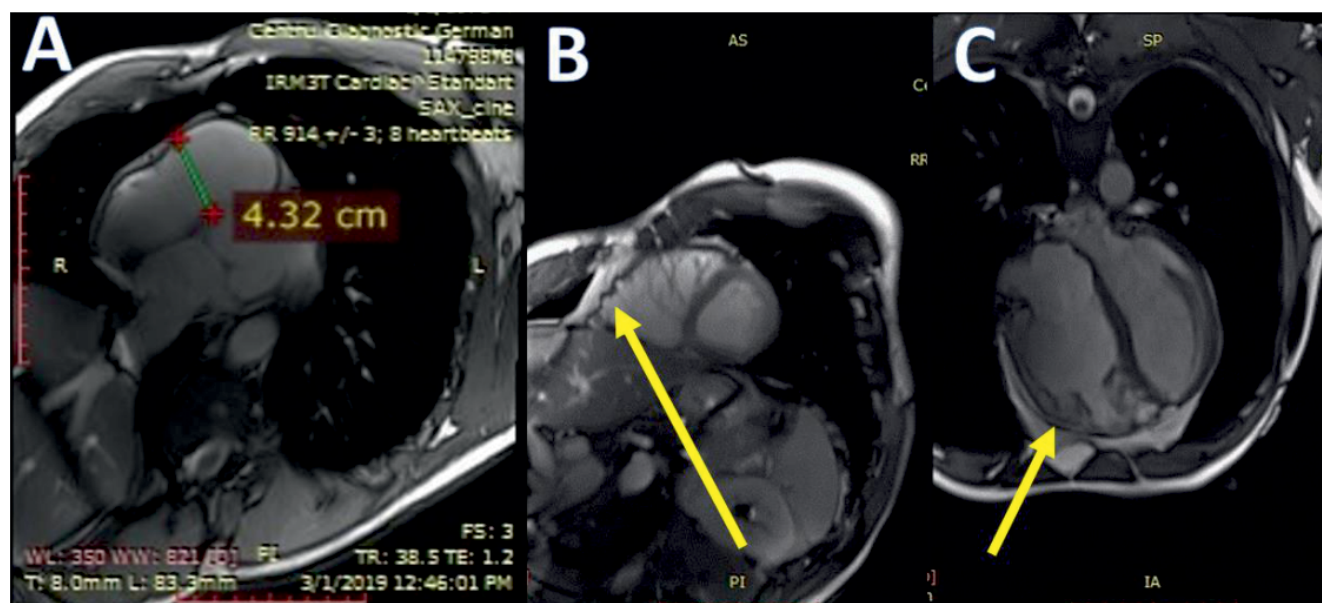


Figure 5. CMR of a 49y old patient with ACM: **A.** RV enlargement, RVOT= 43 mm; **B.** RV aneurysms; **C.** adipose infiltration of the RV free wall.

longitudinal strain rate predicted sudden death/ ventricular tachycardia with a sensitivity up to 88% and a specificity of 77%¹⁶. Speckle-tracking imaging is also useful in the prognostic stratification of first-degree relatives of patients with ACM. Normal RV deformation was correlated with no disease progression during follow-up, while abnormal RV deformation in early stages of ARVC was associated with disease progression¹⁷.

In spite of all the discussed advantages, two-dimensional transthoracic echocardiography has a limited role in the diagnosis of ACM, because regional anomalies of the right ventricular free wall can be often missed. On this matter, intracardiac ultrasound and transesophageal echocardiography have similar diagnostic value as CMR, as they can better identify localized aneurysms, bulges and saculations¹⁸.

In the attempt to overcome previous limitations, CMR has evolved into the main imaging tool for ACM diagnosis (Figure 5). Transmural RV late gadolinium enhancement (LGE) in two orthogonal planes and LV myocardial LGE in a „stria” pattern involving more than one segment are major criteria for the diagnosis of ACM¹. In the early stages of the disease, the LV infero-lateral wall and the peritricuspid area can be the only regions involved. LGE can detect myocardial scars in the LV infero-lateral wall even in these stages, thus being an extremely important diagnostic tool¹⁹.

The positive diagnosis of ACM is often burdened by the presence of the so called „ACM mimics”, which can either be normal variants mimicking the disease or

other pathological conditions. CMR is the gold standard for the evaluation of RV volumes and function, due to its superior spatial resolution and tissue characterization. From 2481 CMR examinations, among which 124 were performed for suspected ACM, 4% of patients had ACM imaging criteria and 13% of the findings were consistent with ACM mimics. Moreover, when compared with TTE, CMR was superior in the recognition of ACM mimics (13% versus 1%)²⁰. Other CMR studies reported a prevalence of ACM mimics between 4.4% and 5%^{21,22}. In a small study that included 51 patients (20 with ACM, 11 athletes and 20 controls), echocardiographic criteria as established by both TFC and ASE, were not able to differentiate between ACM patients and athletes²³. Another study that compared 34 healthy athletes with 34 ACM patients and 8 trained athletes with ACM using CMR, aimed to assess the diagnostic efficiency of RV end-diastolic volume (RVEDV) and RV EF and the additional value of strain analysis. RVEDV was not decisive for the positive diagnosis of ACM, as almost 95% of the athletes fulfilled the criteria on RV dilatation. However, strain and strain rate values of the midventricular RV free wall were significantly lower in the ACM group²⁴.

The LV phenotype in biventricular ACM can be easily confused with that of dilated cardiomyopathy (DCM) and CMR also proved useful in the differential diagnosis of these two entities. In a study that included 87 patients with ACM and 153 patients with DCM, LV-LGE was present in all patients with ACM and LV systolic dysfunction and only in 45% of patients with

DCM. In addition, the extent of LGE was significantly greater in patients with ACM-LV phenotype and a LV-LGE $\geq 20\%$ had a 100% specificity for ACM with LV involvement. The distribution of LGE was also different in the two groups, affecting more often the subepicardial layers in ACM and the midmural layers in DCM¹¹.

Feature Tracking Cardiovascular Magnetic Resonance (FT-CMR) allows the calculation of myocardial strain values and plays a central role in the evaluation of RV pathology. FT-CMR is superior to other strain analysis techniques through its shorter post-processing times and it is operator dependent to a smaller extent. All available software methods are capable to distinguish ACM patients from controls by global strain. Moreover, subtricuspid region strain is abnormal in ACM patients for all software methods, thus emphasizing the possible role of FT-CMR in the early diagnosis of ACM²⁵. CMR-FT also proved useful in the detection of impaired LV global and regional peak systolic strain in patients with ACM and preserved LV EF, thus identifying the LV involvement more rapidly. In addition, LGE in LV myocardium is detected by CMR-FT even in patients with preserved LV EF and this can possibly imply the presence of fibro-fatty infiltration in the LV myocardium. RV altered mechanics could contribute to the appearance of LV dysfunction in patients with ACM. Among 68 ACM patients, RV global radial strain was significantly associated with LV global and regional longitudinal peak strain¹⁰. Moreover, CMR strain is significantly lower in the cicatricial myocardial segments and lower strain values are superior to LGE in the detection of the arrhythmogenic substrate, thus serving in the early identification of patients with ACM at increased risk for ventricular arrhythmias²⁶.

In addition, CMR can detect myocardial fat infiltration and fibrosis, both of them with important prognostic value. Native T1 mapping is a hopeful imagistic tool for the detection of diffuse fibrosis. In a study that included 43 patients with ACM (13 genotype-positive patients with ACM according to 2010 Task Force Criteria, 17 genotype-positive at-risk relatives without fulfilling Task Force Criteria and 13 control subjects), LV LGE was documented in 69% overt patients, 41% of the relatives and in no controls. Both mean LV T1 and T1 dispersion were significantly higher in overt patients. In addition, when compared to control patients, T1 dispersion was significantly greater in relatives, mainly secondary to elevated times in LV inferior and posterolateral regions. In this manner, asymptomatic patients could be identified before the advance-

ment to an apparent clinical phenotype²⁷. In another study that included 175 patients with ACM as defined by the International Task Force in 2010, an abnormal CMR was in all cases associated with the appearance of SCD, resuscitated cardiac arrest or appropriate implantable cardiac defibrillator firing. Moreover, LV involvement at CMR alongside non-sustained ventricular tachycardia were independent risk factors for hard cardiac events²⁸.

Finally, CMR could serve in the early detection of different genetic forms of ACM and in the individualizing of the therapeutic approach. In a study that included 44 patients with ACM who were evaluated by CMR and classified according to their genetic condition (desmosomal mutation, non-desmosomal mutation or negative), LV-LGE pattern did not differ between the three groups, with a dominant subepicardial enhancement. However, patients with non-desmosomal mutations had significantly greater rates of an annular or circumferential subepicardial LV-LGE pattern. Moreover, patients with desmosomal mutations had higher RV-LGE, when compared to the two remaining groups²⁹.

Although not included in the current diagnostic criteria¹, cardiac CT has the ability to detect RV dilatation, wall motion abnormalities, an indented RV surface, trabecular enlargement, as well as the presence of adipose infiltration. Moreover, regional wall motion abnormalities evaluated by multidetector CT were concordant to those assessed by MRI or echocardiography. 4D-cine CT can accurately assess the complex anatomy of the RV, as well as the degree of fatty infiltration of the RV wall. Thus multidetector CT could be a reasonable alternative in patients in which the MRI is less likely to be performed⁵. PET-CT can be useful in differentiating ACM from sarcoidosis³⁰.

It is well known that the quantification of adipose tissue could have a great prognostic value, as advanced stages of ACM were associated with more extensive epicardial fat. In a study that included 44 patients with ACM and 45 controls, cardiac CT was used in order to evaluate different distributions of adipose tissue: intra-thoracic, mediastinal and total epicardial adipose tissue. The amount of adipose tissue inside the visceral pericardium was significantly higher in patients with ACM. Moreover, there was more adipose tissue localised around LV and RV in patients with ACM, when compared to controls, with no differences regarding total intrathoracic adipose tissue or atrial adipose tissue. Thus, LV epicardial fat could also help in the di-

agnosis of ACM with up to 71% specificity and 91% sensitivity³¹.

Radionuclide angiography may be useful in the assessment of RV EF, RV volume, and the standard deviation of regional times of end systole. Abnormal myocardial sympathetic function evaluated by single-photon emission computed tomography has been correlated with the recurrence of ventricular arrhythmias⁸.

The diagnosis of ACM is challenging particularly because of its heterogeneity in presentation, which varies from focal RV involvement to biventricular or prominent LV phenotype. Additionally, even with the widespread availability of modern imaging techniques, there is still a lack of awareness in the health care community and this pathology persists in being under- or misdiagnosed. Given the limited indication of endomyocardial biopsy for the diagnosis of ACM¹, one can conclude that the progress that has been made in the last few years in the multimodality imaging field is of utmost importance for the early detection and proper treatment of patients with ACM, providing valuable prognostic information.

Conflict of interest: none declared.

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