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REVIEW

Risk markers in arrhythmogenic cardiomyopathy

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Abstract: Arrhythmogenic cardiomyopathy is an autosomal dominant inherited cardiomyopathy that predispose to malignant arrhythmic events and heart failure. Arrhythmic risk stratification is manly based on arrhythmic history and phenotype severity. Implantation of a cardiac defibrillator is the only effective strategy to prevent sudden cardiac death. Survival have been improved once implantable cardioverter-defibrillator has been extensively used and the number of malignant ventricular arrhythmias survivors developing heart failure has substantially increased. Heart failure develops more often in the setting of left ventricle or biventricular involvement. Left ventricle dysfunction and heart failure are associated with specific genotype. Serial longitudinally follow-up of arrhythmogenic cardiomyopathy patients reported development of new criteria over time and progressive ventricular dilatation and dysfunction as well as development of full arrhythmogenic cardiomyopathy phenotype over time in mutation-positive family members. Recognition of risk markers is important in the setting of arrhythmogenic cardiomyopathy for an optimal management.
Keywords: arrhythmogenic cardiomyopathy, arrhythmias, heart failure, sudden cardiac death, risk markers

Rezumat: Cardiomiopatia aritmogenă este o cardiomiopatie moștenită cu transmitere autozomal dominantă care predispune la evenimente aritmice maligne și la insuficiență cardiacă. Stratificarea riscului aritmic se bazează în principal pe istoricul de aritmii și pe severitatea fenotipică. Impantul de cardiodefibrilator este unica strategie eficientă pentru prevenția morții cardiace subite. Supraviețuirea a fost îmbunătățită o dată cu folosirea extensivă a cardiodefibrilatorului implantabil și astfel numărul supraviețuitorilor de aritmii ventriculare maligne care ajung la insuficiență cardiacă a crescut substanțial. Insuficiența cardiacă apare mai frecvent în contextul afectării ventriculare stângi și a afectării biventriculare. Disfuncția ventriculară stângă și insuficiența cardiacă sunt asociate cu anumite genotipuri. Urmărirea longitudinală a pacienților cu cardiomiopatie aritmogenă a raportat apariția de criterii noi de-a lungul timpului, a dilatației și disfuncției ventriculare progresive ca și a dezvoltării de fenotip complet de cardiomiopatie aritmogenă la membri de familie purtători de mutație genetică. Recunoașterea markerilor de risc este importantă în contextul cardiomiopatiei aritmogene pentru un management optim.
Cuvinte cheie: cardiomiopatia aritmogenă, aritmii, insuficiență cardiacă, moarte cardiacă subită, markeri de risc

INTRODUCTION

Arrhythmogenic cardiomyopathy (AC), an autosomal dominant inherited cardiomyopathy, results from desmosomal gene mutations, mechanical uncoupling, cell detachment, progressive myocytes death and subsequent fibrofatty tissue replacement of the ventricular myocardium[1].

Natural history of the disease has been derived from outcome studies which showed that AC has 2 main outcomes: malignant arrhythmic events (sudden cardiac death (SCD), ventricular fibrillation(VF)/ sustained ventricular tachycardia (SVT), appropriate implantable cardioverter-defibrillator (ICD) therapy) and more rarely heart failure (HF) (end-stage HF, HF death and cardiac transplantation).

Several clinical phases of the disease have been described: a concealed phase with subtle structural changes and risk of sudden cardiac death, a second phase of clinical overt disease with right ventricle (RV) functional and structural abnormalities in addition to arrhythmias, a third phase of severe RV dilatation and dysfunction with right HF and preserved left ventricle (LV) function and a forth phase of biventricular involvement and dysfunction which mimic dilated cardiomyopathy[2].

In addition, there have been described 3 pattern of disease expression: classic pattern with isolated RV

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disease and LV involvement in the advanced phase of the disease, predominant LV involvement form and biventricular pattern with paralleled biventricular impairment[3].

AC has a heterogeneous progression, from long-term favorable course to ventricular life-threatening arrhythmias and progressive right and biventricular dilatation and dysfunction finally leading to HF.

EVALUATION OF ARRHYTHMIC RISK IN ARRHYTHMOGENIC CARDIOMYOPATHY

As electrical instability is present from early disease phases, cardiac arrest due to malignant arrhythmias may occur as the first manifestation of the disease in young, previously healthy and asymptomatic individuals.

Studies that sought predictors of life threatening arrhythmic events had different designs[4]. Many studies sought predictors of arrhythmic outcome as a composite measure of SCD, resuscitated SCD, VF/SVT, appropriate ICD therapy[5-7]. Other studies focused on identifying predictors of appropriate ICD therapy in patients with primary prevention implanted ICD[8,9] or in patients with both primary and secondary implanted ICD[10-12]. There were also research groups that studied the composite outcome of cardiovascular death[13] or the composite outcome of major adverse cardiovascular events such as cardiac arrest, heart transplantation, survived SCD, VF, SVT and arrhythmic syncope[14-16].

Arrhythmic risk stratification is manly based on arrhythmic history and phenotype severity. An international task force consensus document defined 3 groups of patients according to their arrhythmic risk 17 (Table 1). High-risk patients received a class I indication of ICD implantation, intermediate-high group received a class IIa indication of ICD implantation, intermediate-low group received a class IIb indication and low-risk patients received a class III indication of ICD implantation[17]. A recent study[18] evaluated the performance of the *International Task Force Consensus Statement Risk Stratification* Algorithm[17]. This study concluded that the algorithm accurately differentiated survival from any sustained ventricular arrhythmia (VA) among different categories although the incidence rate was higher than estimated for patients in class I and class IIa indication; the algorithm did not differentiated survival free from ventricular fibrillation/flutter between high risk and intermediate-high risk groups[18]. Nevertheless, more important than differentiation of arrhythmic risk between class I and class IIa is to define patients who have a low enough arrhythmic risk so that ICD implantation can be deferred and unnecessary complications avoided[19].

While there is general agreement that a history of resuscitated sudden cardiac death and VF/hemodynamically unstable VT confers the highest risk of SCD, the association of other risk markers with SCD depend on the studied population[20]. Regardless of the phenotypic expression, male sex, syncope, T-wave inversions beyond V3, RV dysfunction and NSVT/SVT are risk markers of arrhythmic outcome. History of exposure to strenuous exercise and VT inducibility at electrophysiological study are additional risk markers in borderline AC patients. In AC mutation carriers, the list of arrhythmic predictors is extended by including the presence of symptoms, multiple mutations, ventricular ectopy and LV dysfunction[20].

Conventional echocardiographic methods are useful in assessing regional wall motion abnormalities, global RV dysfunction and RV dilatation and global LV dysfunction and LV dilatation[21]. Alternatively, the same parameters can be assessed by cardiac magnetic reso-

Table 1. Arrhythmic risk stratification in arrhythmogenic cardiomyopathy (modified after Corrado et al.[17])

High arrhythmic risk (estimated rate of life-threatening arrhythmic events >10%/year)		Aborted SCD due to VF, history of SVT, severe RV dysfunction[a], severe LV dysfunction[b]
Intermediate arrhythmic risk (estimated rate of life-threatening arrhythmic events 1-10%/year)	Intermediate-high arrhythmic risk	At least one major risk factor: • syncope, NSVT, moderate RV[c] dysfunction, moderate LV dysfunction[d]
	Intermediate-low arrhythmic risk	At least one minor risk factor: • frequent ventricular ectopy, inducible VT at EPS, male, complex genotype, young age, T wave inversion beyond V3
Low arrhythmic risk (estimated rate of life-threatening arrhythmic events <1%/year)		Patients without any risk factors and healthy gene carriers.

Abbreviations: SCD=sudden cardiac death; VF=ventricular fibrillation; SVT=sustained ventricular tachycardia; RV=right ventricle; LV=left ventricle; NSVT=nonsustained ventricular tachycardia; VT=ventricular tachycardia; EPS=electrophysiological study.
[a]Severe RV dysfunction=RV fractional area change ≤17% or RV ejection fraction≤35%;
[b]Severe LV dysfunction=LV ejection fraction ≤35%;
[c]Moderate RV dysfunction=RV fractional area change 17-24% or RV ejection fraction 36-40%;
[d]Moderate LV dysfunction=LV ejection fraction 36-45%.

nance (CMR) with higher spatial resolution[22]. In addition, ventricular function can be assessed by speckle tracking echocardiography[21]. Peak systolic myocardial strain by 2D speckle tracking echocardiography from 3 RV free wall segments is averaged as a measure of RV longitudinal strain (RVLS) and from 16 LV segments is averaged as a measure of LV global longitudinal strain (LV GLS). Alternatively, RV peak systolic longitudinal strain values from 6 segments are averaged to calculate RV global longitudinal strain (RV GLS). This has lower absolute values compared with RVLS[21]. Temporal parameters such as time-to-peak strain can be also assessed. Mechanical dispersion is measured as the standard deviation of the time from onset R on ECG to maximum LV and RV shortening by strain in a 6 RV segment and a 16 LV segment model respectively. Diagnosis of the disease and risk stratification are a composite of familiar, ECG, arrhythmic history, histological, functional and structural features[21].

Thus, future guidelines regarding management of AC patients need to include a calculator of arrhythmic risk based on individual characteristics of the patient that can help the clinician to make decisions regarding ICD implantation.

Implantation of a cardiac defibrillator is the only effective strategy to prevent SCD while antiarrhythmic and ablation therapy improve symptoms and quality of life by reducing arrhythmic recurrences and ICD discharges[23]. Thus, reducing the risk of SCD by properly risk-stratifying patients who would benefit from an ICD is vital.

HEART FAILURE

The other important outcome of AC is end-stage HF and heart transplantation. While refractory VT storm are rarely the indication for cardiac transplantation in AC, refractory end-stage HF is usually the reason for transplanting AC patients[24]. Survival have been improved once ICD implantation has been extensively used and the number of malignant VA survivors developing HF has substantially increased. It is reasonable to consider asymptomatic AC patients as stage B heart failure patients, monitor development of HF symptoms and manage risk factors[25] in order to prevent or delay the onset of HF[26]. Fewer studies have focused on searching predictors of progression toward end-stage HF. Progression toward ventricular dilatation and dysfunction seems to be a slow process[27] and onset of signs/symptoms might be insidious. Usually patients with AC who receive transplants for HF have prolonged clinical course[28]. One recent study described HF in the setting of AC and reported predictors of HF[29]. In this cohort, women had a higher risk of HF independent of the presence of LV involvement; lateral precordial T-wave inversions predicted HF and particularly symptomatic LV dysfunction. Patients who developed signs and symptoms of HF before presentation had less arrhythmic burden and therefore a milder arrhythmic phenotype. Desmosomal desmoplakin (DSP) and digenic heterozygosity were associated with LV dysfunction and HF[29,30] and nondesmosomal phospholamban mutation[27,31] was associated with LV involvement in several studies. It was reported that young age at presentation (Figure 1) and LV involvement are associated with need for cardiac transplantation in the setting of AC[28,32].

DISEASE PROGRESSION

Initially it was thought that AC was due to a development defect of RV myocardium but it has been shown that myocardial atrophy is in fact a consequence of progressive myocytes loss that begins after birth and evolves thereafter[2]. Furthermore, genetic testing and familial screening showed that relatives who present with subclinical phenotype are at risk of developing manifest AC over time[33]. Electrocardiographic studies[34,35] and serial imaging examinations that longitudinally followed AC patients reported development of new repolarization/depolarization criteria[36] over time (Figure 2) and progressive ventricular dilatation and dysfunction[37,38].

Among asymptomatic family members, mutation positive female siblings had the strongest probability to fulfill definite AC diagnosis at last follow-up[33]. Development of full AC phenotype (definite AC diagnosis) over time in family members has been predicted by symptomatic status at enrollment and abnormal baseline ECG[39].

Classically, it has been considered that electrical abnormalities precedes structural abnormalities[39]. But it has been shown that subtle structural alterations detected through altered RV deformation pattern can occur before electrocardiographic changes[40]. And the substrate of altered RV deformation pattern is reduced local contractility and increased local passive stiffness of the myocardium[40]. Electrocardiographic abnormalities reflect the interference of fibrofatty tissue with electrical impulse conduction. ECG may have lower accuracy in detecting early abnormalities than deformation parameters from advanced imaging

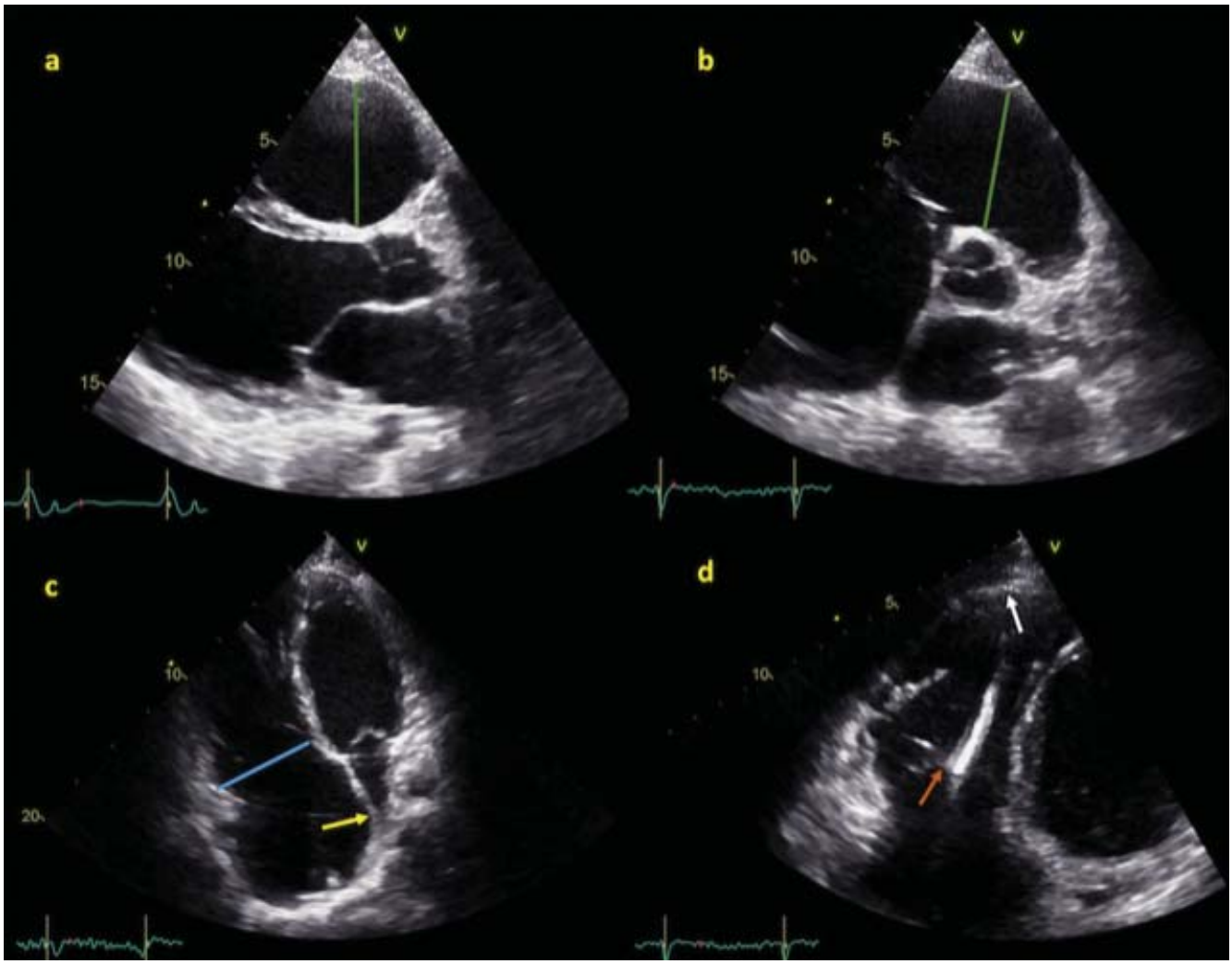

Figure 1. PKP2 mutation positive patient, diagnosed at 17 years old with arrhythmogenic cardiomyopathy, with history of high exercise intensity exposure (10 METs) has been transplanted at 26 years old for end-stage heart failure. Echocardiographic study before heart transplantation shows: **Panel a:** PLAX view shows increased RVOT diameter 4,9 cm (vertical green line). **Panel b:** PSAX view shows increased RVOT diameter 5 cm (green line). **Panel c:** Apical 4 chamber view shows increased basal RV diameter 5,1 cm (blue line) and leftward bulging of atrial septum (yellow arrow). **Panel d:** RV focused apical 4 chamber view shows thin-walled akinetic apical segment of RV free wall (white arrow) and ICD lead visible in RV cavity (orange arrow).
Abbreviations: PKP2 = plakophilin-2; PLAX = parasternal long axis view; PSAX = parasternal short axis view; RVOT = right ventricle outflow tract; RV = right ventricle; ICD = implantable cardioverter-defibrillator.

techniques. Indeed, in family members, abnormal RV deformation at baseline predicted disease progression, primarily development of new electric criteria during follow-up[41].

For patients diagnosed in the phase of overt disease who already fulfill the majority of 2010 *Revised Task Force Criteria*[36], disease progression continues toward severe RV dilatation and dysfunction with right HF and further toward a phase of biventricular involvement and dysfunction which mimic dilated cardiomyopathy[2]. In a cohort of definite AC patients of which two thirds had structural task force criteria from baseline, significant RV structural progression was predicted by depolarization criteria at baseline while significant LV structural progression was predicted by the presence of phospholamban mutation[27].

The prognostic significance of development of new repolarization, depolarization or arrhythmic criteria over time has not been defined. One study have shown an association between significant structural RV progression and occurrence of the first ICD therapy during follow-up[27].

In conclusion, recognition of risk markers is important in order to prevent SCD, but current therapeutic approach do not prevent the development or progression of the disease.

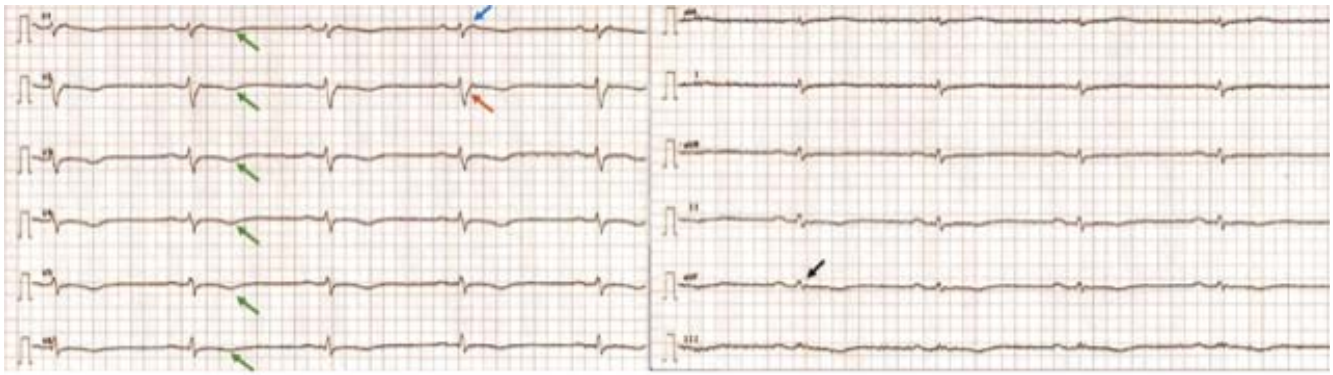

Figure 2. 12-lead electrocardiogram of 47 years old PKP2 mutation positive patient with arrhythmogenic cardiomyopathy shows:
- T wave inversion in precordial leads (green arrows) (major repolarization Revised 2010 Task Force criteria);
- epsilon wave (blue arrow) (major depolarization Revised 2010 Task Force criteria);
- terminal activation duration ³ 55 msec (orange arrow) (minor depolarization Revised 2010 Task Force criteria);
- Fragmented and low-amplitude QRS complexes in limb leads (black arrow).

Conflict of interest: none declared.

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