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Prevention of sudden cardiac deaths in arrhythmogenic right ventricular cardiomyopathy: How to evaluate risk and when to implant a cardioverter-defibrillator?

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Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined myocardial disease resulting in fibrofatty degeneration of myocardium. Most known mutations associated with the development of this disease affect genes responsible for coding information on desmosomal proteins. The primary function of these proteins is to form intercellular junctions. Disruption of desmosomes invariably leads to cell death, and resulting tissue remodeling impairs electrical conduction creating conditions for re-entry. The natural history of ARVC involves three clinical stages [1, 2]:

— initial asymptomatic phase;
— focal structural changes with electrical instability;
— global impairment of contractility with symptomatic heart failure.

The incidence of ARVC is estimated at 1:5,000 to 1:10,000. The disease usually manifests at young age, mostly in the second or third decade of life. Patients present with ventricular arrhythmia followed later by symptoms of heart failure. Cardiac arrest may also be an initial presentation. Studies show that ARVC is one of the most common causes of sudden cardiac death in young, apparently healthy people, accounting for 5–11% of sudden deaths in subjects below 35 years of age [3]. The disease is more common among men, although gender seems not to affect the risk of sudden cardiac death. Most fatal cases occur in the fourth decade of life (mean age 35.5 ± 12.0 years), and yearly mortality rate is about 2.8%, with 1/3 of deaths occuring suddenly and the remaining 2/3 due to advanced heart failure [4].

ARVC is also one of the most common causes of sudden deaths during sport participation. According to some authors, up to 22% of sudden deaths among athletes may be related to this form of cardiomyopathy. Studies performed in the 1980s in a large population of competitive athletes in Italy showed that intensive physicial training is associated with a 5-fold increase in risk of a sudden cardiac death.

Sudden deaths in ARVC usually occur during daily life activities (76% of cases), stressful situations (10%) or in the perioperative period (10%). Only 3.5% of deaths occur during intensive physical activity, which is likely related to a limited number of subjects participating in competitive sports [3].

Evaluation of risk

Evaluation of risk factors of sudden cardiac death in ARVC should include [1, 3]:

— previous episodes of cardiac arrest;
— syncope;
— a history of sudden cardiac death in a family member below 35 years of age;
— extensive right ventricular damage;
— concomitant left ventricular dysfunction;
— induction of ventricular tachycardia during programmed electrical stimulation;
— wide QRS complexes in V1–V3, QRS dispersion, and the presence of epsilon wave (a marker of ventricular late potentials).

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How to identify patients at highest risk of sudden death? According to most authors, the strongest risk factor is history of previous cardiac arrest or syncope [3]. Opinions on the relative importance of other risk factors are discordant. Long-term data presented by a group of French authors indicate high risk of sudden cardiac death in patients with severe righ ventricular dysfunction and symptomatic right-sided heart failure, as well as in patients with concomitant left ventricular dysfunction and recurrent sustained ventricular tachycardia [2]. Some authors suggest that apart from clinical symptoms of heart failure, additional electrocardiographic (ECG) criteria should also be taken into account, such as the presence of negative T waves in leads V4–V6. Another risk factor of sudden cardiac death in ARVC is QRS dyspersion ≥ 40 ms (specificity 90%, sensitivity 77%). The risk of sudden death seems to be particularly high in patients with QRS dyspersion ≥ 50 ms, negative T waves in precordial leads, and a history of syncope [3, 5].

Analysis of risk factors may be supported with data collected from patients with an implanted cardioverter-defibrillator (ICD). These data show that appropriate ICD therapy was most common in patients with such risk factors as severe right ventricular dysfunction, previous cardiac arrest, history of hemodynamically unstable ventricular tachycardia, young age, left ventricular dysfunction, and induction of a rapid ventricular tachycardia with programmed electrical stimulation during the electrophysiological study [6–9]. Of note, the electrophysiological study itself has little prognostic value in ARVC, as both positive and negative predictive values for the occurrence of malignant arrhythmia do not exceed 50%. This has been reflected in the European Society of Cardiology (ESC) guidelines rating the performance of the electrophysiological study in patients with ARVC as class IIb recommendation (level of evidence: C).

Very useful practical clues may be obtained from the analysis of ECGs recorded during arrhythmia. Most typically, ventricular tachycardia with the left bundle branch block morphology is seen, which is not a risk factor of sudden cardiac death in hemodynamically stable patient with ARVC.

Currently, risk stratification in ARVC is often supplemented by the findings of genetic studies. Variants of the disease associated with significantly higher risk of sudden deaths have beeen identified, such as Naxos disease, which is a recessive form of ARVC occuring predominantly in inhabitants of this Greek island. Another variant of ARVC, observed in inhabitants of Newfoundland, is associated with almost 7-fold increase in risk for male carriers of the mutation in comparison to the female carriers. The most common genetic variants of ARVC in Europe and in the United States result from autosomal dominant mutations of genes for plakophillin-2, desmoplakin, and desmoglein-2, seen in 11–50%, 6–16%, and 10% of patients, respectively. In Poland, the most prevalent mutations occur in plakophillin-2 gene and are associated with a significantly worse prognosis [4].

How to decrease the risk of sudden cardiac death?

The most important advice for patients with ARVC is to refrain from competitive sports. Experimental studies showed that intensive exercise leads to expression of the disease. Chronically increased right ventricular volume load in patients with defective desmosomal proteins results in disruption of abnormal intercellular junctions, which initiates the cascade of apoptotic processes leading to remodelling of myocardium and predisposing to cardiac arrhythmias in the mechanism of re-entry.

In addition to this unfavourable effect on myocardial remodelling, intensive exercise in patients with ARVC may also directly trigger malignant arrhythmia, especially when extreme effort is accompanied by stress, such as during participation in competitive sports. In such conditions, disruption of abnormal intercellular junctions ensues, leading to focal cardiomyocyte necrosis and, when elevated catecholamine levels are present, development of late afterdepolarizations that may result in ventricular fibrillation. This mechanism may also occur in low-risk patients, even in an asymptomatic stage of the disease.

Antiarrhythmic pharmacotherapy in patients with ARVC is quite effective. Good treatment effects are obtained in about 65% of patients, and partial improvement is seen in additional 13% of patients. The most effective drug (in nearly 70% of cases) is sotalol, usually administered in large doses (ranging from 320 to 640 mg/day). Low-risk patients may be treated with beta-blockers, especially if arrhythmia occurs mainly during daily or physical activities [4]. In contrast, werapamil may be indicated in cases of arrhythmias occurring at rest, although this drug is effective only in about 44% of patients. Significant right ventricular dysfunction is an independent predictive factor for the ineffectiveness of antiarrhythmic pharmacoterapy. In patients who do not respond to pharmacoterapy, as well as in patients with recurrent ventricular tachycardia

despite optimal therapy, ablation of the arrhythmic substrate should be considered (class II recommendation in the ESC guidelines, level of evidence: C).

Which patients should be treated with an ICD?

High-risk patients should be protected from sudden cardiac death by ICD implantation. This group primarily includes patients after a cardiac arrest or syncope due to ventricular tachycardia, and patients with a history of unexplained syncope if arrhythmia cannot be excluded as the cause of this syncope. In the ESC guidelines, ICD implantation in patients with documented sustained ventricular tachycardia and/or ventricular fibrillation who receive optimal pharmacotherapy, if their expected survival in a good clinical condition exceeds one year, is a class I recommendation (level of evidence: B). The authors of the guidelines acknowledge that no large randomized clinical trials in patients with ARVC have been published to support this recommendation, but the clinical situation in these patients is thought to be very similar to that of patients after a myocardial infarction, in whom benefits of prophylactic ICD implantation have been well established.

In patients with severe form of ARVC (left ventricular involvement, sudden cardiac death in at least one family member, or unexplained syncope if ventricular tachycardia or ventricular fibrillation cannot be excluded as the cause of this syncope) fulfilling similar general requirements as stated above, e.g. expected survival exceeding one year, ICD implantation is a class IIa recommendation (level of evidence: C).

Low-risk patients, particularly with hemodynamically stable monomorphic ventricular tachycardia, have no indications for ICD implantation and should be treated with pharmacotherapy or ablation. The same applies to patients in whom ICD implantation is indicated but not possible for some reasons (class IIa recommendation, level of evidence: C).

Data from patients with ARVC and implanted ICD show that appropriate ICD therapy accounts for 48–78% of all ICD interventions, including life-saving interventions in 24–50% of cases. If one considers only prophylactic ICD implantations (primary prevention of sudden cardiac death), results are very similar, with appropriate ICD interventions in about 70% of patients, and life-saving interventions reported in about 30% of cases.

Despite these good outcomes, the decision about ICD implantation should always result from careful consideration. Reassuringly, only about 15–30% of all ICD interventions are inappropriate, which usually is triggered either by an arrhythmia that is not a life-threatening one (most commonly atrial fibrillation or supraventricular tachycardia) or results from lead dysfunction or displacement. ICD shocks may be a cause of serious discomfort for the patient, leading even to clinical depression. Moreover, lead implantation in patients with ARVC may be associated with disease-specific problems, including [7]:

— risk of perforation of the thin-walled right ventricle;
— difficulties in accurate lead placement related to low R wave amplitude;
— potentially increased pacing and defibrillation thresholds;
— sensing and pacing abnormalities and increased defibrillation threshold due to progression of the disease.

Should dramatic complications ensue, it may be necessary to implant subcutaneous defibrillating leads or refer a patient for urgent heart transplantation. Fortunately, such scenarios are very rare. Most patients tolerate ICD implantation well, and frequent ICD shocks may be prevented by beta-blockers. In case of insufficient effectiveness of antiarrhythmic treatment, patient's referral for radiofrequency ablation should always be considered.

Summary

Evaluation of the risk of sudden cardiac death and assessment of indications for ICD implantation should be performed individually in each patient, taking into account all aspects of the clinical picture and the experience of the managing physician.

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