End stage of arrhythmogenic cardiomyopathy with severe involvement of the interventricular septum

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Detailed histopathologic, immunohistochemical, and ultrastructural analysis of the heart of a 56-year-old woman with end-stage arrhythmogenic cardiomyopathy with a pathogenic plakophilin-2 mutation is described. The explanted heart revealed severe fibrofatty replacement of nearly the entire right ventricular free wall. The left ventricle was severely affected, and, most remarkable, there was massive involvement of the interventricular septum. Immunohistochemical and electron microscopic findings of intercalated disks revealed areas with a heterogeneous distribution of connexin43 and focal electron microscopic abnormalities among these regions. This case illustrates that arrhythmogenic cardiomyopathy is not limited to the right ventricle but involves the entire myocardium, including the interventricular septum.

KEYWORDS Arrhythmia; Arrhythmogenic right ventricular cardiomyopathy; Cardiac transplantation; Cardiomyopathy; Desmosome; Electrocardiogram; Electron microscopy; Gap junction; Genetics; Immunohistochemistry

ABBREVIATIONS AC = arrhythmogenic cardiomyopathy; **Cx43** = connexin43; **Cx43-NP** = nonphosphorylated connexin43; **DSC2** = desmocollin-2; **DSG2** = desmoglein-2; **DSP** = desmoplakin; **ICD** = implantable cardioverter-defibrillator; **IVS** = interventricular septum; **LBBB** = left bundle branch block; **LV** = left ventricle; **PKG** = plakoglobin; **PKP2** = plakophilin-2; **PLN** = phospholamban; **RV** = right ventricle; **TMEM43** = transmembrane protein 43; **VT** = ventricular tachycardia

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Introduction

Arrhythmogenic cardiomyopathy (AC), also known as arrhythmogenic right ventricular (RV) dysplasia/cardiomyopathy, can present in 4 clinical stages that do not necessarily proceed from one to the other: (1) concealed stage without or with minimal structural disease, although sudden cardiac death may occur; (2) overt stage with structural alterations of primarily the RV and episodes of monomorphic ventricular tachycardia (VT); (3) overt stage with obvious structural biventricular involvement; and (4) end stage of the disease with heart failure.[1–3] Left ventricular (LV) dominant variants have been described.[4]

A distinct histopathologic feature of AC is fibrofatty replacement of the ventricular myocardium. Cardiomyocytolysis and replacement by fibrous and fatty tissue is a process that progresses from subepicardial and midmyocardial layers to endocardium.[3,5] These histopathologic changes in the RV have been described for the LV as well.[6] Remarkably, in AC the interventricular septum (IVS) usually is spared from these alterations,[4,5] although it has been reported in up to 20% of AC autopsy patients with biventricular fibrofatty involvement extending to the IVS.[5]

A tentative mechanism for the clinical phenotype and fibrofatty replacement is mechanical and electrical uncoupling of ventricular cardiomyocytes due to desmosomal dysfunction.[7–12] Desmosomes are proteins in the intercalated disk that connect adjacent cardiomyocytes, thereby providing mechanical integrity and electrical stability.[7–12] Alterations in 5 known desmosomal proteins, plakophilin-2 (PKP2),

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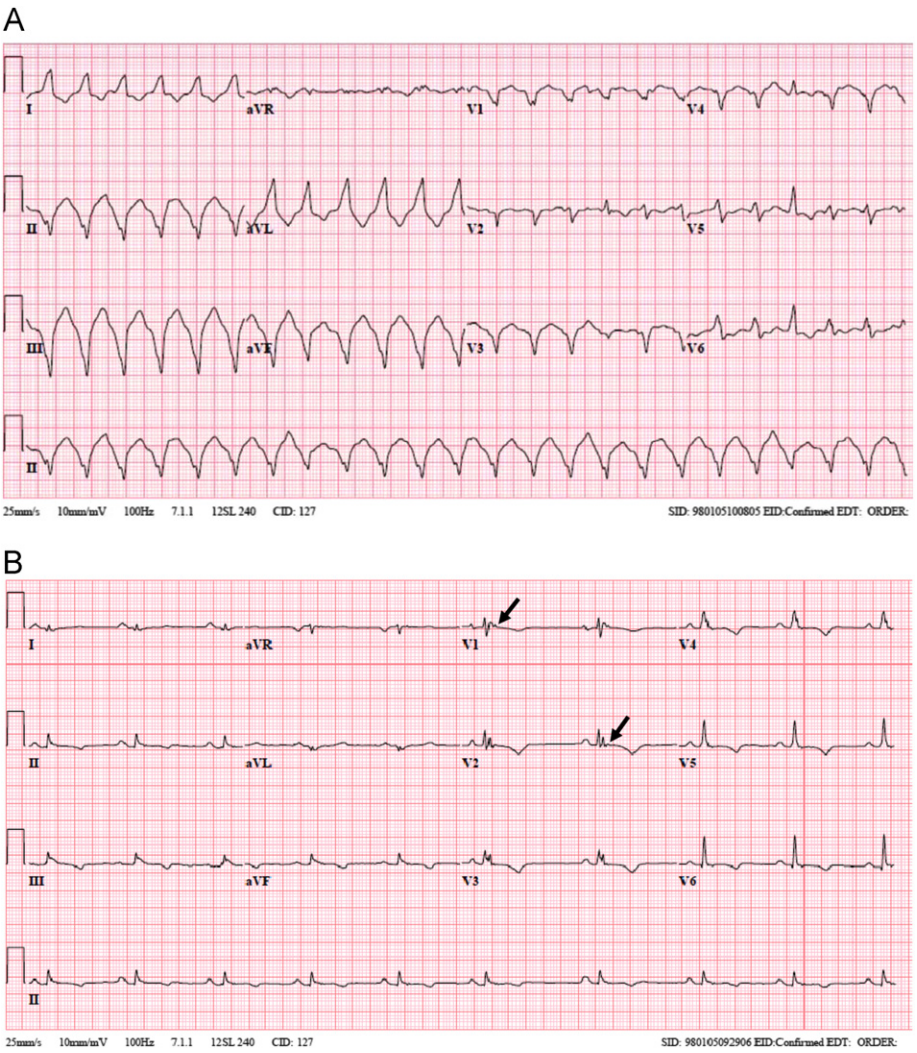

Figure 1 **A:** Twelve-lead electrocardiogram of the index patient showing 1 of 2 morphologies of ventricular tachycardia. **B:** Electrocardiogram of the index patient during sinus rhythm, while off drugs, with epsilon waves (*arrows*) in leads V_1-V_2 and negative T waves in all precordial leads V_1-V_6.

desmoplakin (DSP), plakoglobin (PKG), desmoglein-2 (DSG2), and desmocollin-2 (DSC2), have been related to AC.[13–21] Immunohistochemical analysis can be used to visualize the distribution of desmosomal proteins.[13]

We present the case of an AC patient with a pathogenic *PKP2* mutation undergoing cardiac transplantation because of progressive heart failure. The explanted heart provided the opportunity to study the end stage of the AC disease process in great detail. Macroscopically there was extensive damage to the RV, with LV and remarkably severe septal involvement. Histopathologic, immunohistochemical, and electron microscopy analyses were performed.

Case report

A 56-year-old woman, with a 15-year history of AC, underwent orthotopic cardiac transplantation because of progressive RV and LV failure. In 1995, at age 41 years, a first episode of sustained VT was diagnosed. Sotalol treatment was initiated. Coronary angiography showed no abnormalities, and LV cine angiography showed an aneurysm of the LV apex. VT recurrences occurred in subsequent years, and 2 VT morphologies were recorded: VT1 had a left bundle branch block (LBBB) morphology, extreme superior axis, and cycle length of 320 ms; VT2 also had an LBBB morphology with left superior axis and cycle length of 420 ms (Figure 1A).

The patient was referred to the Utrecht Cardiac Arrhythmia Unit in 1997 because of suspected AC. Diagnosis of AC was confirmed by the presence of epsilon waves in leads V_1-V_3, negative T waves in all precordial leads (Figure 1B), and LBBB VT episodes with superior axis.

Further analysis showed a dilated RV with poor function, and dyskinesia of the RV outflow tract and RV apex on RV cine angiography. During electrophysiologic study, the clinical VT2 was inducible by programmed electrical stimulation. Body surface mapping, pace mapping, activation mapping, and entrainment of the VT confirmed the arrhythmogenic substrate at a right-sided paraseptal inferobasal location. Endocardial radiofrequency ablation was performed, and VT2 was no longer inducible. However, 2 other VT morphologies were inducible after ablation. Clinical VT1 was not inducible at all.

Because of recurrent fast VT episodes during sotalol treatment, an implantable cardioverter-defibrillator (ICD)