VIEWPOINT

Gap junctions and arrhythmogenic cardiomyopathy

Angeliki Asimaki, PhD, Jeffrey E. Saffitz, MD, PhD, FHRS

From the Department of Pathology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts.

Arrhythmogenic cardiomyopathy is the most arrhythmogenic form of human heart disease and a major cause of sudden death in the young.[1,2] It was first described as a right ventricular disease (arrhythmogenic right ventricular cardiomyopathy or ARVC) but is now recognized to include biventricular and left dominant forms that may be misdiagnosed as dilated cardiomyopathy or myocarditis. Arrhythmias occur early in the natural history of arrhythmogenic cardiomyopathy, often preceding structural remodeling of the myocardium.[1,2] This so-called concealed phase of the disease is unique among the primary myocardial disorders. In hypertrophic cardiomyopathy, for example, arrhythmic risk is related to the underlying substrate of myocyte disarray, hypertrophy, fibrosis, and small-vessel disease. And in dilated cardiomyopathy, arrhythmias generally arise in the context of significant ventricular dilatation and contractile dysfunction accompanied by changes in the expression, activity, and spatial distribution of ion channel proteins and currents. In contrast, there is something fundamentally arrhythmogenic about arrhythmogenic cardiomyopathy, particularly in its early stage in which frequent arrhythmias arise in otherwise apparently normal hearts. In this sense, arrhythmogenic cardiomyopathy is more reminiscent of the ion channelopathies than other forms of nonischemic cardiomyopathy.

Arrhythmogenic cardiomyopathy has been linked to mutations in genes encoding desmosomal proteins (*PKP2*, *DSG2*, *DSC2*, *DSP*, and *JUP*).[1,2] Desmosomes are cell–cell adhesion organelles. They are particularly abundant in heart and skin, tissues that normally experience mechanical stress. Not surprisingly therefore, clinical phenotypes in patients with desmosomal mutations take the form of myocardial and cutaneous diseases. In fact, patients with arrhythmogenic cardiomyopathy often exhibit disease flares in response to stress or exercise, emphasizing the importance of biomechanical determinants of disease. However, the relationship between changes in the biomechanical properties of the myocardium produced by desmosomal mutations and heart rhythm abnormalities in arrhythmogenic cardiomyopathy is poorly characterized. Advances in understanding this relationship could reveal important basic mechanisms of arrhythmogenesis.

Dependence of intercellular electrical coupling on intercellular mechanical coupling

As a general rule, defects in intercellular mechanical coupling are associated with an inability to establish and/or maintain normal cell–cell communication via gap junctions.[3] This dependency appears to be especially critical in the myocardium in which large gap junctions, required for safe impulse propagation, are typically surrounded by extensive points of cell–cell adhesion within intercalated disks. The high density of protein packing in gap junctions makes them stiff and susceptible to rupture in response to shear. The intimate juxtaposition of gap junctions and adhesion junctions at intercalated disks may, therefore, have evolved to protect gap junctions from mechanical stress associated with contraction.[3]

Multiple lines of evidence support the idea that normal electrical coupling at gap junctions depends on normal mechanical coupling at intercalated disks. For example, when adult cardiac myocytes are disaggregated and allowed to reassociate, the first connections formed are adherens junctions and desmosomes.[4] Gap junctions appear only after stable mechanical coupling has been reestablished. Genetic interventions that reduce the expression of gap junction proteins have no apparent effect on the number or size of mechanical junctions,[5] whereas genetic ablation of adhesion junction proteins causes a significant reduction in gap junction number and size and increases the risk of arrhythmias.[6] If mutations in desmosomal genes compromise cell–cell mechanical coupling in arrhythmogenic cardiomyopathy, then it follows that gap junction remodeling might be a fundamental feature of the myocardium in this disease. Surprisingly, little is known about whether and how disease-causing desmosomal mutations affect the biomechanical properties of the myocardium, but as detailed below, diffuse gap junction remodeling, demonstrable even during

KEYWORDS Gap junctions; Arrhythmogenic cardiomyopathy

ABBREVIATIONS **ARVC** = arrhythmogenic right ventricular cardiomyopathy; **Cx43** = connexin 43; **TNFα** = tumor necrosis factor α (Heart Rhythm 2012;9:992–995)

Address reprint requests and correspondence: Dr Jeffrey E. Saffitz, MD, PhD, Department of Pathology, Beth Israel Deaconess Medical Center, and Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215. E-mail address: jsaffitz@bidmc.harvard.edu.

1547-5271/$ -see front matter doi:10.1016/j.hrthm.2011.11.024

the concealed phase, appears to be a frequent feature of arrhythmogenic cardiomyopathy.

Gap junction remodeling in arrhythmogenic cardiomyopathy

Gap junction remodeling in arrhythmogenic cardiomyopathy was first described in 4 patients with Naxos disease, a rare cardiocutaneous syndrome with the clinical triad of woolly hair, palmoplantar keratoderma, and ARVC caused by a recessive deletion mutation in the gene encoding the mechanical junction protein plakoglobin (also known as γ-catenin).[7] The amount of immunoreactive signal for the major ventricular gap junction protein, connexin 43 (Cx43), was found to be markedly reduced at intercalated disks in right and left ventricular myocardia. One of these patients was known to carry the recessive mutation and exhibited the characteristic hair and skin features of the disease, but died at age 7 years of acute nonlymphocytic leukemia. At autopsy, the heart appeared normal (Figure 1). However, Holter monitoring had documented frequent ventricular extrasystoles mainly of right ventricular origin, and progressive depolarization abnormalities including QRS prolongation and epsilon waves (Figure 1).[7] Immunofluorescent analysis showed a marked reduction in the amount of Cx43 signal in the heart, and immunoblotting showed an apparent loss of highly phosphorylated Cx43 (Figure 1), which is known to be selectively located within gap junctions as opposed to intracellular sites. Electron microscopy showed fewer and smaller gap junctions at intercalated disks, thus confirming the immunohistochemical findings.[7] Although demonstrated in only a single example of concealed disease, these observations suggest that gap junction remodeling occurs early in the natural history of arrhythmogenic cardiomyopathy before the onset of myocardial degeneration and fibrofatty tissue accumulation.

Gap junction remodeling has also been reported in the heart in Carvajal syndrome, another cardiocutaneous syndrome characterized by woolly hair, palmoplantar kerato-

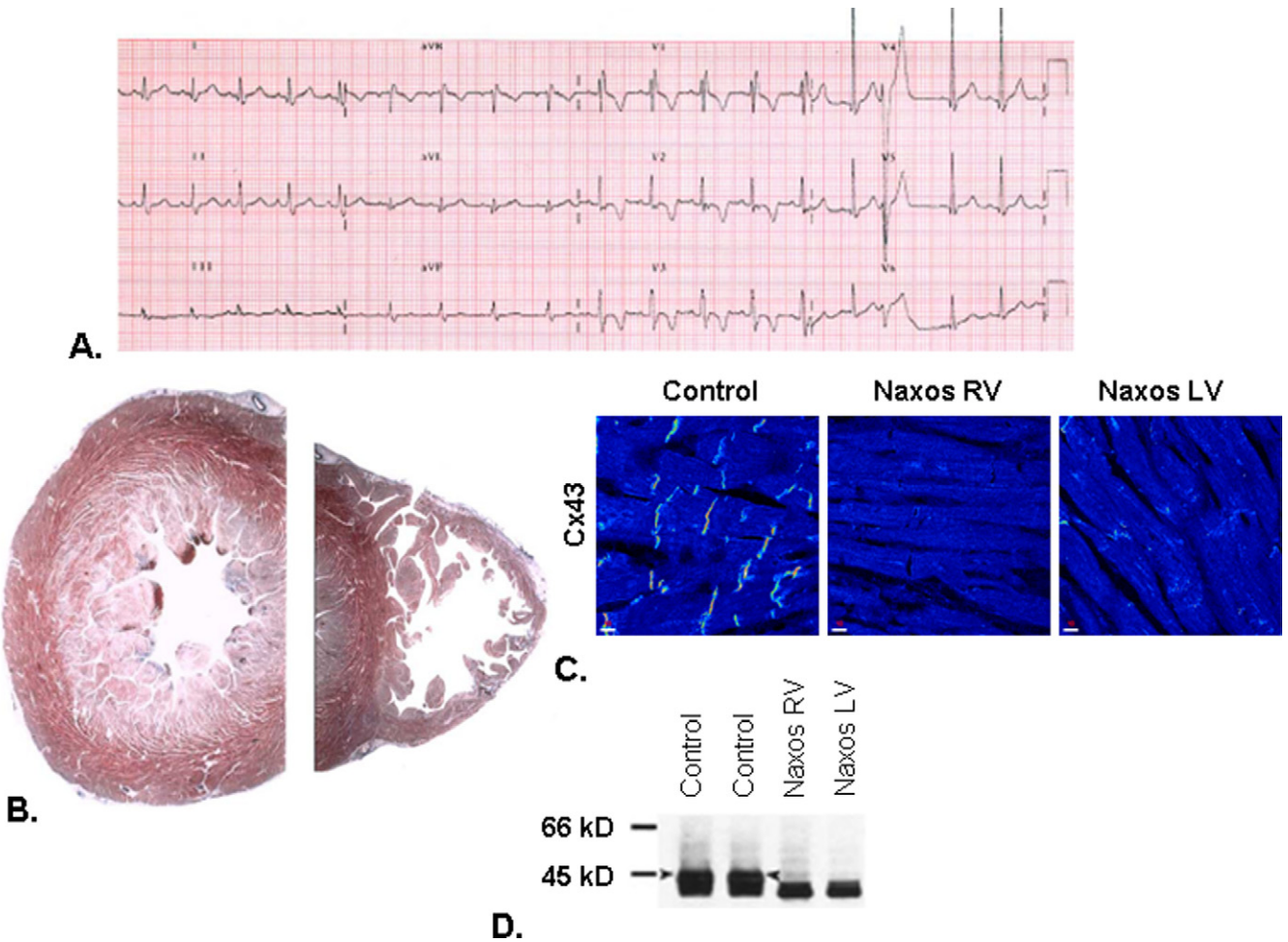

Figure 1 **A:** Twelve-lead electrocardiogram at rest from a 7-year-old patient with Naxos disease in the "concealed phase" showing QRS prolongation (to 110 ms) and epsilon waves in leads V1 through V3 and deeply inverted T waves in leads V1 through V3. **B:** Low magnification sections of left and right ventricles at autopsy showing no evidence of myocardial degeneration or fibrofatty tissue accumulation (trichrome Heidenhain stain). **C:** Representative confocal images showing loss of immunoreactive Cx43 signal at intercalated disks in the left ventricle of this patient compared with a normal control. **D:** Immunoblot of Cx43 in left and right ventricular myocardia of this patient showing an apparent loss of highly phosphorylated Cx43 (arrows) compared with a normal control. Modified from Kaplan et al.[7] Cx43 = connexin 43; LV = left ventricle; RV = right ventricle.