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Cardiovascular Pathology 21 (2012) 229–239

CARDIOVASCULAR PATHOLOGY

Review Article

# Arrhythmogenic cardiomyopathy: from autopsy to genes and transgenic mice (SCVP Achievement Award Lecture, San Antonio, TX, February 27, 2011)

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Received 9 September 2011; accepted 30 September 2011

**Abstract**

We present the history of arrhythmogenic cardiomyopathy since its discovery in the 1980s at autopsy of young subjects, who died suddenly during effort as a first manifestation of the disease and in whom the right ventricle was found as the source of lethal arrhythmias. Most of the contributions have come from the Padua as well as from the Paris and London schools.

Investigations were then developed to arrive at the diagnosis, and these include electrocardiography, angiography, echocardiography, electroanatomic mapping, endomyocardial biopsy, and magnetic resonance imaging. Disqualification from sport activity and implantable cardioverter defibrillator proved to be life-saving.

Genetic investigations have confirmed that arrhythmogenic cardiomyopathy is a hereditary Mendelian disease, either dominant or recessive, with mutations of genes encoding intercellular proteins (desmosome disease).

The disease was recently reproduced in transgenic mice, with electrocardiographic and morphologic features overlapping the human disease.

Cardiomyocyte cell death occurs with time as a genetically determined injury. The challenge now is to find ways to prevent onset and progression of the disease. 

*Keywords:* Arrhythmogenic cardiomyopathy; Autopsy; Transgenic mice

Mr President, dear colleagues,

It is a sign of destiny that I am receiving this honor in San Antonio. As you know, I come from Padua, the town where St. Anthony, formerly lecturer in theology at the University of Bologna, died and was buried in 1231 and is venerated worldwide as "il Santo." The Franciscan friars, who arrived in this land of North America in 1691 on June 13, named the river "Rio San Antonio" because it was the anniversary of St. Anthony's death. Certainly, they could not predict that three centuries later a scholar from the University of Padua would be lecturing here about science rather than about theology, although my name is also the same as that of a renowned saint of the Renaissance-era Catholic Counter-Reformation, San Gaetano Thiene.

I have chosen as the topic of my talk today the history of the investigations carried out in Padua on arrhythmogenic right ventricular cardiomyopathy, to which I devoted a large part of my scientific interest (Fig. 1).

Italy may rightly claim the discovery of the disease as a distinct heredofamilial morbid entity. In 1736, Giovanni Maria Lancisi [1] published posthumously in Naples the book *De Motu Cordis et Aneurysmatibus*. Lancisi was professor of anatomy at the University "La Sapienza" in Rome and the personal doctor of the Pope (*Archiater Pontificius*). In chapter V of his book, entitled "De Hereditaria ad Cordis Aneurysmata

Part of this article was published in Thiene G, Corrado D, Bauce B, Basso C, "Arrhythmogenic right ventricular cardiomyopathy: a historical overview." *Cardiac Electrophysiology Clinics* 2011;3:179–191, with permission of the editor.

This study was supported by the Registry for Cardio-Cerebrovascular Pathology, Veneto, Venice, Italy.

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1054-8807/11/$ – see front matter 
doi:10.1016/j.carpath.2011.09.012

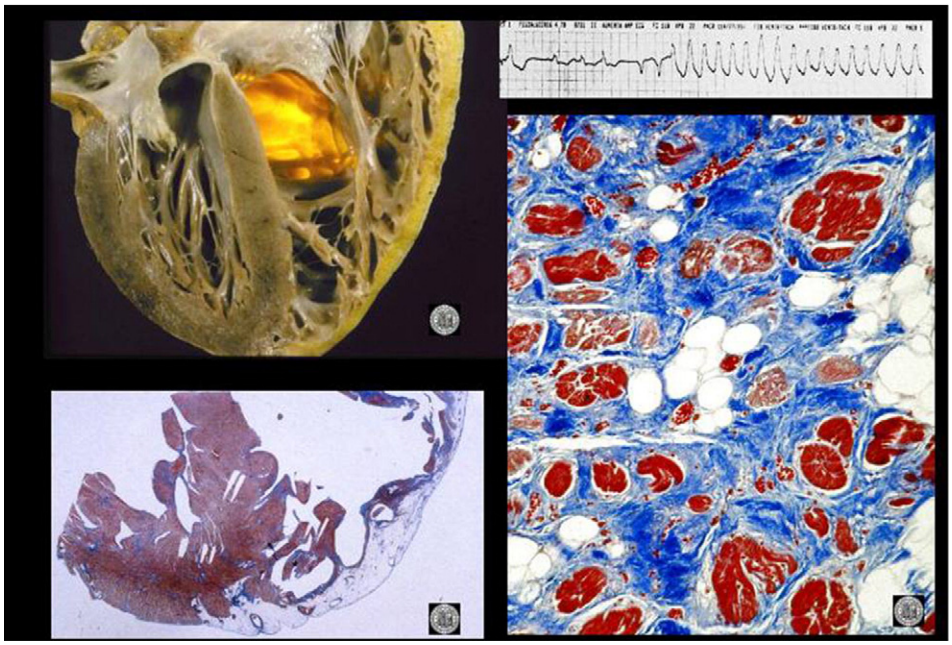

Fig. 1. Gross, histologic, and ECG features of arrhythmogenic cardiomyopathy.

Constitutione: De Cordis Prolapsu" ("On the Hereditary Predisposition to Cardiac Aneurysms: Cardiac Prolapse), he reported some examples of such morbid entities and described the history of a family with disease recurrence in four generations, all featured by signs and symptoms which were in keeping with what today is known as arrhythmogenic cardiomyopathy (AC): palpitations, dilatation and aneurysms of the right ventricle (RV), heart failure, sudden death. Thus, the first description of AC dates back nearly two and a half centuries ago, a lot earlier than modern observations.

In 1905, Sir William Osler [2] reported a case of a nearly 40-year-old man who died suddenly while climbing a hill. Postmortem examination disclosed a biventricular myocardial atrophy, with a thinning and translucency of the ventricular free walls that Osler immortalized with the name "parchment heart." The heart specimen is part of the Maude Abbot collection [3]. Segall [4] in 1950 reviewed the specimen and republished the case with unequivocal drawings showing paper-thin walls.

A controversial case, which was the source of subsequent misconceptions, has been reported by Uhl [5] at the Johns Hopkins Hospital in Baltimore in 1952. He published the article, "A previously undescribed congenital malformation of the heart: almost total absence of myocardium of the right ventricle," about an 8-month-old female infant who died due to congestive heart failure and no arrhythmias on ECG. Here is the description of the heart at autopsy: "… almost the entire dilated chamber (RV) was occupied by a large laminated mural thrombosis which adhered firmly to the endocardium along the anterior wall of the ventricle. Examination of the cut edge of the ventricle wall revealed it to be paper-thin with no myocardium visible… In the RV wall epicardium and endocardium lie adjacent to each other with no intervening cardiac muscle…" and no fibro-fatty tissue in the RV free wall was observed. The early age and the peculiar pathological description point to a structural heart disease present at birth (congenital malformation), as emphasized by the title itself. Clinical presentation was neither characterized by cardiac arrhythmias nor by a family history of heart disease. Thereafter, cases in adults with paper-thin ventricular walls have been published with the eponym of Uhl's anomaly, clearly a misnomer since the parchment heart in adults is the end stage of a late progressive loss of the myocardium followed by fibro-fatty replacement.

At the University of Padua, pages have been written that are milestones in the history of the disease [6]. Sergio Dalla Volta [7,8] in 1961 and 1965 first published similar cases under the name of "auricularization of the RV pressure" to emphasize the behavior of the RV chamber without an effective systolic contraction and with the blood pushed to the pulmonary artery, mainly thanks to the right atrial systole. Although the patients presented also with ventricular arrhythmias, Dalla Volta concentrated more on the hemodynamic features rather than on the arrhythmogenicity of the RV. One of the original patients reported by Dalla Volta underwent cardiac transplantation 30 years later in 1995 at the age of 65, because of congestive RV failure. The left ventricle was normal, whereas the RV was hugely dilated with diffuse paper-thin free wall and complete disappearance of the myocardium [9] (Fig. 2).

Similar observations were performed by Paolo Rizzon [10] at the University of Bari in 1965. In 1968, Froment et al. [11] published two anatomo-clinical cases with a clearcut evidence of fibrofatty replacement of the RV free wall at histology.

Again at the same institution (University of Padua), the pathologist Vito Terribile in 1972 performed an autopsy on a