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Review article

# Science and practice of arrhythmogenic cardiomyopathy: A paradigm shift

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> "A paradigm shift is a change in basic assumptions (paradigms) within the frame work of the theories of sciences"[1]
>
> Thomas Kuhn, The structure of scientific revolutions, 1962.

## INTRODUCTION

The clinical, genetic, and molecular paradigm of arrhythmogenic right ventricular cardiomyopathy (ARVC) has markedly progressed through the last three decades, shifting from the classical ARVC as a progressive condition characterized by fibrofatty replacement of the right ventricle,[2,3,4] into a wider spectrum of arrhythmogenic cardiomyopathy (AC),[5] which covers ARVC with its various clinical phases (occult, electric, right heart failure and late stage biventricular heart failure), biventricular arrhythmic cardiomyopathy, left dominant arrhythmic cardiomyopathy, Naxos and Carvajal syndromes. Epidemiologically, the disease was first associated with the Mediterranean basin (mainly Italy and France), however further studies have reported AC in many races and ethnic backgrounds.[6,7,8] Moreover, with regard to the pathoitiology of the disease, dysplasia was originally assumed as the disease mechanism. Other mechanisms were later postulated, such as inflammation and transdifferentiation. However, more recent animal models have established that dystrophy, either by myocyte necrosis or apoptosis, is the founding pathological process of AC. In addition, in 1994 when the first genetic locus mutation was described, the researchers were investigating chromosome 14, as it was thought that ARVC and hypertrophic cardiomyopathy (HCM) may have a similar genetic background.[9] The paradigm, however, shifted towards desmosome mutations as the genetic basis of AC in 2000 with the discovery that mutations in plakoglobin and desmoplakin cause the cardio-cutaneous autosomal recessive forms of the disease, i.e., Naxos and Carvajal syndromes.[10,11] In this work, we will shed some light on the progress of the many faces of AC: pathology, molecular, genetics, clinical, electrophysiology, imaging, risk stratification and management.

## INCIDENCE

AC incidence is estimated to be 1 in 2,500 to 5,000 in the general population, with male predominance.[12] It is considered one of the major causes of sudden cardiac death (SCD) in the young and young athletes.[3] Athletes affected with AC represent an especially high risk SCD group.[13]

## PATHOLOGY

The pathological diagnosis of AC has been traditionally based on the gross and histological evidence of transmural myocardial loss with fibrofatty replacement of the right ventricle (RV) free wall, extending from the epicardium toward the endocardium.[3] Gross morphological findings of AC include focal areas

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of severe muscle thinning that may transilluminate under a light source, local or global ventricular cavity enlargement, and ventricular wall aneurysms. Aneurysms are only present in 20 to 50% of autopsy cases of AC.[14,15] RV aneurysms, located in the triangle of dysplasia (inflow, apex, outflow tract), are considered pathognomonic for AC.[2] However, autoptic features of AC may range from grossly normal hearts, in which only a careful histopathological investigation can reveal AC features, up to massive RV and/or LV involvement. Therefore, the existence of cases with biventricular involvement or predominantly with LV or RV involvement suggest the use of the more comprehensive term AC.[16,17]

Histological examination reveals islands of surviving myocytes interspersed within fibrous and fatty tissue. Clusters of dying myocytes provide evidence of the acquired nature of myocardial atrophy, and are frequently associated with inflammatory infiltrates (Figure 1).[16] Rather than being a continuous

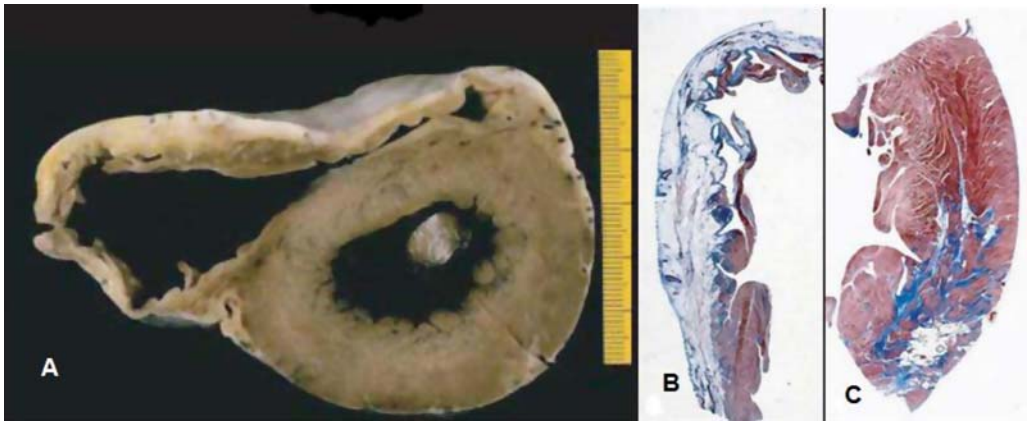


**Figure 1. Arrhythmic cardiomyopathy pathology. A: Cross section of a heart of a 17 year old male who died suddenly during a football match. Note the right ventricular dilatation, fibro-fatty replacement and anterior and posterior wall aneurysms. B: Histology of the right ventricular free wall of the same patient showing transmural fibrofatty replacement. C: Histology of the left ventricular free wall showing focal subepicardial left ventricular involvement. (Modified from Thiene, G., Corrado, D. & Basso, C. Arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Orphanet journal of rare diseases* 2, 45 (2007).**

process, disease progression may occur in periodic bursts. Environmental factors, such as exercise or inflammation, may facilitate onset and progression of myocyte loss and fibrofatty replacement.[18] The deposition of adipose tissue is a peculiarity of AC, however its specificity has been controversial. Significant fat infiltration of the RV is reported in more than 50% of normal hearts in the elderly.[19] It has been recently suggested that isolated adipose replacement of the RV myocardium should only be considered pathological if observed in association with myocytes at various stages of cell death.[20]

## PATHOGENESIS

Many theories have been postulated to explain the mechanism of the loss of the ventricular myocardium and its substitution by fibrous and fatty tissue: dysplasia, myocarditis, transdifferentiation, and dystrophy. The original concept of the disease as congenital abnormality (dysplasia, aplasia, or hypoplasia) characterized with maldevelopment of RV myocardium.[2] This led to the historical confusion in literature about AC and Uhl's anomaly. Henry Uhl, at the Johns Hopkins Hospital in Baltimore, in 1952, reported a case of an almost total absence of the myocardium of the RV in a 7-month-old infant. The epicardium and endocardium lay adjacent to each other, with no intervening cardiac muscle and no fibrofatty tissue observed in the RV free wall.[21] On contrary, in AC, myocardial death occurs after birth, usually during childhood, and is progressive with time. Another theory was the inflammatory process; with myocardial loss due to infective or immune mechanisms. Cardiotropic viruses, such as adenovirus, hepatitis C virus, and parvovirus B19, have been reported in the myocardium of some AC patients.[22] However, the viral agent might be just an innocent bystander or play a secondary role to the progression of myocardial loss. Transdifferentiation of myocytes into fibrocytes and/or adipocytes has also been proposed.[23] This theory is questionable because of the limited de-differentiaton capabilities of adult cardiomyocytes. Myocyte dystrophy remains the most likely explanation to the AC pathological process. Similar to skeletal muscle dystrophy observed in

Duchenne or Becker diseases, a progressive and acquired myocardial atrophy – with replacement by exuberant fatty and fibrous tissue – occurs in the hearts of AC patients. This dystrophy, either by apoptosis or necrosis, could account for a genetically determined loss of myocardium.[15,18,24] Transgenic animal models have been recently developed, supporting the dystrophy theory. A transgenic mouse with cardiac-restricted overexpression of the C-terminal mutant (R2834H) desmoplakin has been shown to develop increased cardiomyocte apoptosis, myocardial fibrosis, and lipid accumulation as well as biventricular dilatation/dysfunction.[25] In another seminal study of a transgenic mouse model (Tg-NS) with cardiac overexpression of desmoglein-2 gene mutation N271S, clinical features of AC, as well as, myocyte necrosis were obsereved in all Tg-NS hearts.[26]

## ROLE OF DESMOSOMES IN ARRHYTHMIC CARDIOMYOPATHY PATHOGENESIS

Desmosomes are a specific type of cell junction within intercalated discs, the specialized intercellular junctions of cardiomyocytes (Figure 2). They form membrane anchorage sites for intermediate

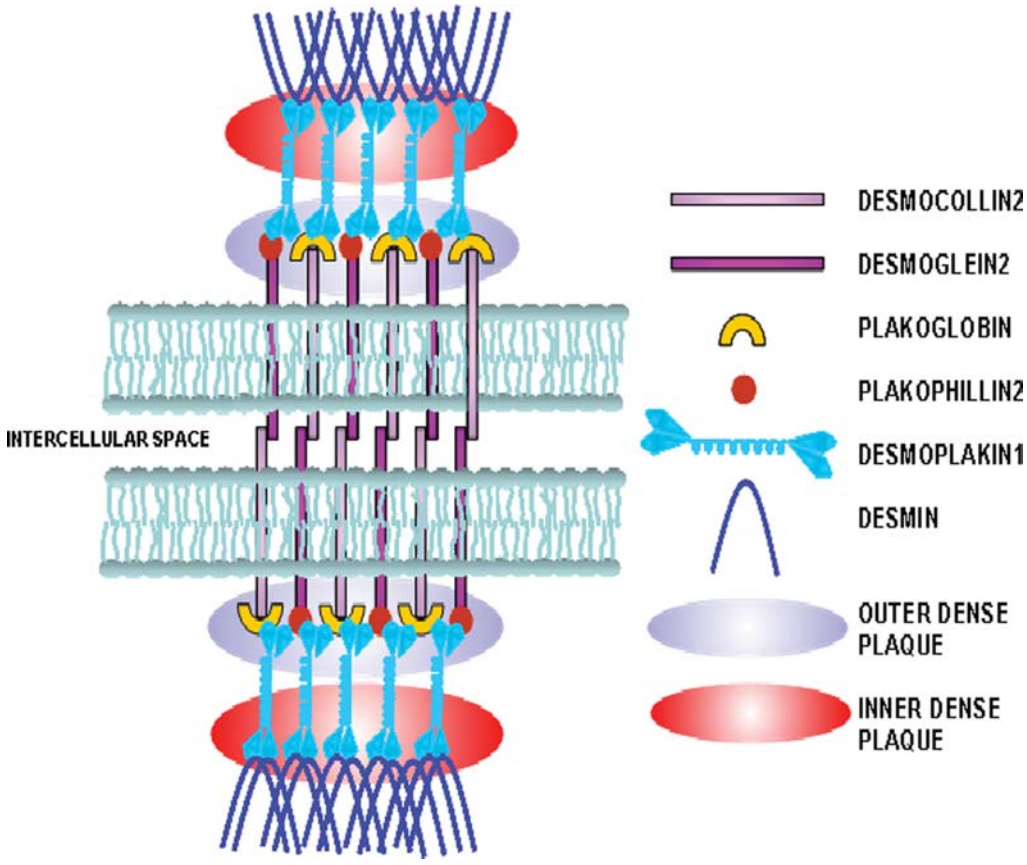


**Figure 2. The desmosome consists of three families of proteins: the desmosomal cadherins, desmocollin and desmoglein, members of the armadillo family of proteins, plakoglobin and plakophillin and the plakins. Binding of these proteins tethers desmin intermediate filaments to the plasma membrane in cardiac myocytes and adheres adjacent myocytes together.**

filaments, and the resulting complex is thought to impart tensile strength and resilience. The cardiac desmosomes have been proposed to support structural stability through cell-cell adhesion, to regulate adipogenesis and apoptosis related genes, and to maintain proper electrical conductivity through the regulation of gap junctions and $Ca^{2+}$ homeostasis. Functionally, desmin forms intermediate filaments in mature striated muscle that surround the Z discs and link the entire contractile apparatus to the sarcolemmal cytoskeleton, cytoplasmic organelles and nucleus. Desmoplakin (DSP) and junctional plakoglobin (JUP) are constituents of the submembranous plaques of the desmosomes, along with plakophillin (PKP), and they form part of the link between the intermediate filament cytoskeleton and the cytoplasmic tail of cadherins. The desmosomal cadherins are calcium-dependent cell adhesion

glycoproteins, divided in two classes namely, the desmoglein (DSG) and the desmocollin (DSC), and they mediate lateral and transcellular desmosomal adhesion (Figures 2 and 3).

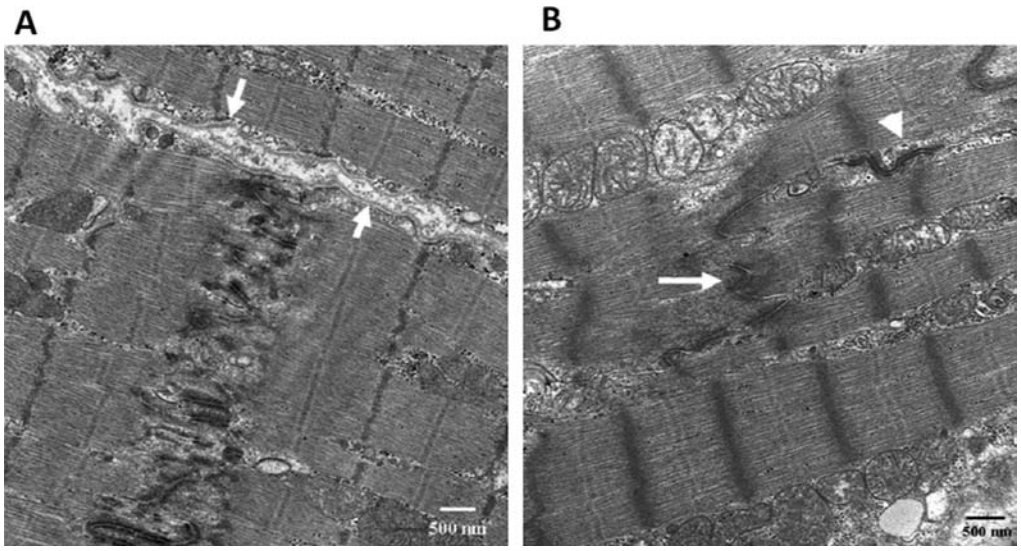


**Figure 3. Electron microscopic view of cardiac myocyte intercalated discs. (A) Normal case control. Regular cell membrane (arrows) and intercalated disc between adjacent myocytes. (B) ARVC patient with desmoplakin gene splice site mutation. Note the abnormal position of long desmosomes (arrowhead) and the widened gap of facia adherens (arrow). Original magnification: X15 000. Adapted from Basso C. *et al.* Ultrastructural evidence of intercalated disc remodelling in arrhythmogenic right ventricular cardiomyopathy: an electron microscopy investigation on endomyocardial biopsies. *Eur Heart J* 27, 1847–1854 (2006).**

A desmosomal protein alteration may compromise either cell-to-cell adhesion and/or intermediate filament (desmin) function. The right ventricle with its thinner wall and higher distensibility is particularly vulnerable to the impaired cell adhesion. In contrast, disruption of intermediate filament (desmin) binding, such as in desmoplakin mutation since it is directly interacting with desmin, may result in dominant and/or severe left ventricular involvement. In either case, this mechanical disintegration will eventually lead to significant ventricular myocyte loss, especially during higher volume state loads, as for example, during sports activity. Because the regenerative capacity of the myocardium is limited, repair by fibrous or fibrofatty replacement takes place. This fibrofatty islands are the substrate for macro-reentry ventricular arrhythmias. Re-entrant tachyarrhythmias circle around the fibrous tissue and into an isthmus of surviving myocytes, in a figure-of-8 fashion similar to that occurring around ischemic myocardial scars. Moreover, disruption of desmosomal integrity per se can alter the electric stability of the myocytes, regardless of the extent of myocyte loss. For example, it has been recently demonstrated that PKP2 associates with sodium voltage gated channels Na(V)1.5, and that knockdown of PKP2 expression alters the properties of the sodium current, and the velocity of action potential propagation in cultured cardiomyocytes.[27]

## HERITABILITY

AC cases have been shown to have a genetic component, with approximately one-third to one-half of them being familial. The inheritance pattern is autosomal dominant, i.e. both mutation homozygotes as well as heterozygotes can develop AC, although rare autosomal recessive cases – where only mutation homozygotes can present with the disease – have also been reported.[4,28] AC-causing mutations have variable expressivity, with highly-variable phenotypes, ranging from severe disease with early death, to individuals who were completely asymptomatic late in life, even among family members carrying the same gene mutation.[29,30] Penetrance is incomplete (20-30% or higher), with a significant percentage of the mutation carriers not presenting with an unaffected, normal phenotype.[31] Interestingly, gender may have an influence on penetrance, with male mutation carriers more likely to develop specific phenotypic manifestations of this disease.[14] The reduced penetrance along with variable expressivity, suggest that other genetic modifiers and/or environmental factors are implicated in disease

pathogenesis. At the genetic counseling level, these characteristics make it difficult to trace the disease along a family line and to identify the members at risk of carrying a mutation.

## GENETICS

AC-causative mutations have been identified in ten different genes, although two of these (TGFB3 and RYR2) are rarely associated with AC. Four additional genes associated with autosomal dominant AC have been mapped but not identified (locus names ARVD3, ARVD4, ARVD6, and ARVD7). Molecular genetic testing is clinically available for eight of the ten known genes (Table 1). Since AC is emerging a

**Table 1. Arrhythmogenic right ventricular dysplasia (ARVD) gene loci**

| Disease locus | Gene Name | Gene Symbol | Chromosome location | Frequency |
|---|---|---|---|---|
| ARVD1 | transforming growth factor beta-3 | TGFB3 | 14q24 | Rare |
| ARVD2 | ryanodine receptor 2 | RYR2 | 1q42 | Rare |
| ARVD5 | transmembrane protein 43 | TMEM43 | 3p25 | Unknown |
| ARVD8 | desmoplakin | DSP | 6p24 | 6-16% |
| ARVD9 | plakophilin-2 | PKP2 | 12p11 | 11-43% |
| ARVD10 | desmoglein-2 | DSG2 | 18q12 | 12-40% |
| ARVD11 | desmocollin-2 | DSC2 | 18q12 | Rare |
| ARVD12 | junction plakoglobin (or gamma catenin) | JUP | 17q21 | Rare |

desmosome related disease (eight of ten genes are desmosome related), desmosome gene mutations accounting for approximately 50% of symptomatic individuals,[32] and compound and digenic heterozygosity being often encountered, screening of all desmosomal AC related genes is now recommended.[33] Among the different desmosome genes, mutations have been identified in desmoplakin (DSP), plakophilin-2 (PKP-2), desmoglein-2 (DSG-2), desmocollin-2 (DSC-2), junction plakoglobin (or gamma catenin) (JUP), and more recently in plakophilin-4 and desmin.[17,34]

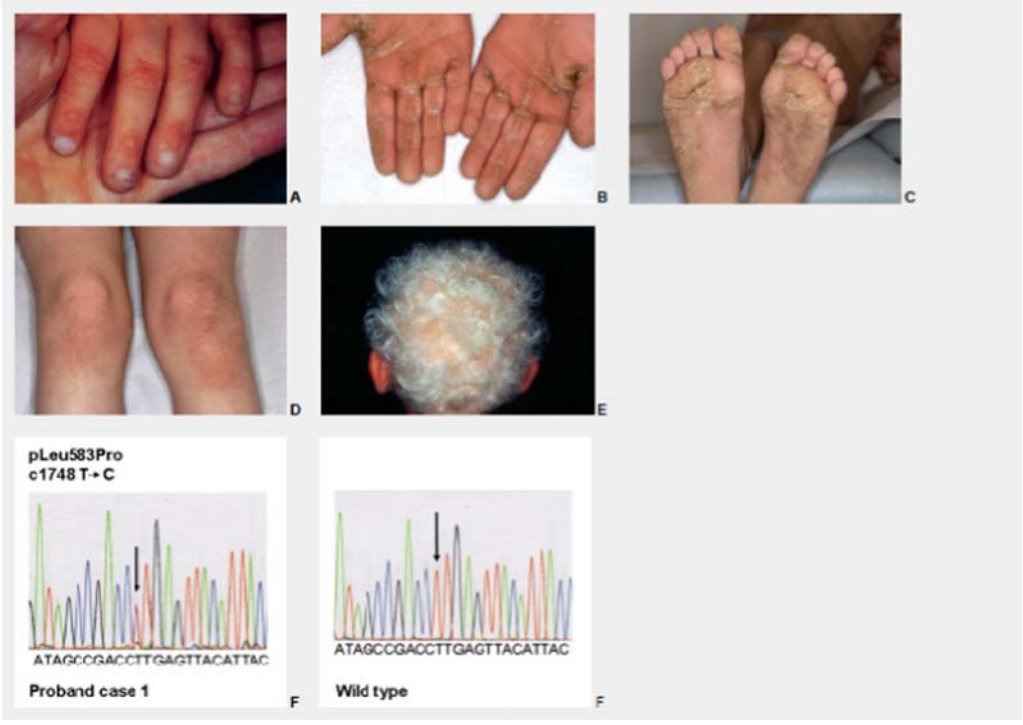


**Figure 4. Deramological phenotype and genetic screening of a case of Cardiocutaenous syndrome (Carvajal). A: Dystrophic nail plates. B: Striate keratoderma of the palms. C: Plantar keratoderma, C: Erythemato-squamous skin lesions of the knee. E: curly wooly hair. F: Electropherograms of the desmoplakin mutation and of the wild type: a heterozygous variant in *DSP*, c.1748 T > C, was identified, resulting in the missense mutation p.Leu583Pro at a heterozygous state. From: Keller, D. *et al.* De novo heterozygous desmoplakin mutations leading to Naxos-Carvajal disease. *Swiss medical weekly* 142, (2012).**

**Table 2. Revised 2010 Task Force critiria for diagnosis of ARVC. Definite diagnosis: 2 major or 1 major and 2 minor criteria or 4 minor from different categories; borderline: 1 major and 1 minor or 3 minor criteria from different categories; possible: 1 major or 2 minor criteria from different categories. Adapted from Marcus F *et al.* Diagnosis of arrhythmogenic right ventricular cardiomyopathy/ dysplasia. Proposed Modification of the Task Force Criteria. Eur Heart J 31, 806 – 814 (2010)**

| | |
|---|---|
| 1-Right ventricular structural and functional abnormalities by: | Major:-<br>- Regional wall akinesia, dyskinesia, or aneurismal dilatation of the RV<br>Plus one of the following :- |
| A- Echocardiography | - Right ventricular out flow tract of 19 mm/m2 in parasternal long axis view at the end diastole, 21 mm/m2 in parasternal short axis view at the end diastole<br>- Change of fractional area by less than 33%.<br>Minor:-<br>-Regional wall akinesia or dyskinesia<br>Plus one of the following :-<br>- Right ventricular out flow tract of 16 to19 mm/m2 in parasternal short axis view at the end diastole or 18 to 21 mm/m2 in parasternal short axis view at the end diastole<br>- Change of fractional area more than 33% but less than 40%. |
| B- Cardiac magnetic resonance | Major:-<br>- Regional wall akinesia or dyskinesia or dyssynchronous contraction plus one of the following:<br>- Ejection fraction less than 40%,<br>- End-diastolic volume t more than 110 mL/m2 ,or more 100 mL/m2 in males and females, respectively.<br>Minor:-<br>- Regional wall akinesia or dyskinesia or dyssynchronous contraction plus one of the following:<br>- Ejection fraction more than 40% but less than 45%.<br>-end-diastolic volume more than 100 to but less than 110 mL/m2 or more than 90% but less than 100% in males and females, respectively |
| C- Right ventricular angiogram. | Major:-<br>- Regional wall akinesia, dyskinesia, or aneurysmal dilatation |
| 2-Characteristics of right ventricular wall tissue by Endomyocardium biopsy. | Major:-<br>- The total amount of the residual myocytes are less than 60% by morphometric analysis (or less than 50% if estimated), and the remaining of the free wall myocardium are replaced by fibrous tissue with or with out fatty changes in more than one sample.<br>Minor:-<br>- The total amount of the residual myocytes are 60% to 75% by morphometric analysis (or 50% to 65% if estimated), and the remaining of the free wall myocardium are replaced by fibrous tissue with or with out fatty changes in more than one sample. |
| 3- Electrocardiographic repolarization abnormalities. | Major:-<br>-Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete right bundle-branch block QRS > 120 ms).<br>Minor:-<br>-Inverted T waves in leads V1 and V2 in individuals >14 years of age (in the absence of complete right bundle-branch block) or in V4, V5, or V6<br>- Inverted T waves in leads V1, V2, V3, and V4 in individuals >14 years of age in the presence of complete right bundle-branch block. |
| 4-Electrocardiographic depolarization abnormalities. | Major:-<br>-Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3).<br>Minor:-<br>- Late potentials by Signal Avereged ECG in >1 of 3 parameters in the absence of a QRS duration of >110 ms on the standard ECG.<br>- Filtered QRS duration (fQRS) >114 ms.<br>- Duration of terminal QRS,40 mV (low-amplitude signal duration) >38 ms<br>-Root-mean-square voltage of terminal 40 ms <20 mV<br>- Terminal activation duration of QRS >55 ms measured from the nadir of the S wave to the end of the QRS, including Ro, in V1, V2, or V3, in the absence of complete right bundle-branch block. |
| 5- Arrhythmias | Major:-<br>- Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL).<br>Minor:-<br>- Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III,and aVF and negative in lead aVL) or of unknown axis.<br>- >500 ventricular extra systoles per 24 hours (Holter). |

| | |
|---|---|
| 6-Family history of ARVC. | Major:-<br>- Positive family history of first-degree relative confirmed by current task force criteria.<br>- Pathological confirmation of the disease in first-degree relative either by autopsy or surgery.<br>- Discovering of a DNA pathogenic mutation that has been recognized to be associated or probably associated with ARVC in the patient who has been evaluated for ARVC.<br>Minor:-<br>-Positive family history of first-degree relative in whom the diagnosis is not feasible to be confirmed by current Task Force criteria.<br>-Positive family history of young (<35 years) first degree relative with sudden death due to suspected ARVC.<br>- Positive family history of disease in second degree relative who has been confirmed to have the disease either by current Task Force Criteria or pathologically. |

Of note, mutations in some of these genes have been associated with genetically related (allelic) disorders. Specifically, RYR2 mutations have been identified in individuals with catecholaminergic polymorphic ventricular tachycardia (CPVT),[35,36] as well as patients with "atypical" or "borderline" long QT syndrome (LQTS) who did not have mutations identified in the five genes associated with LQTS.[37] DSP mutations can lead to Carvajal syndrome, an autosomal recessive disease characterized by ventricular dilated cardiomyopathy associated with keratoderma and woolly hair[38,11,39] (Figure 4), while JUP mutations can be causative of Naxos disease, an autosomal recessive form of ARVD characterized by palmoplantar keratoderma and peculiar woolly hair that was first observed on the island of Naxos, Greece.[10,40] Historically, it was the phenotype of woolly hair and palmoplantar keratoderma in those two syndromes that pointed scientists towards screening desmosomal genes for pathogenetic mutations. Interestingly, as opposed to other AC subgroups, Naxos disease has full penetrance by adolescence.[41]

Ongoing efforts are aiming to identify genotype-phenotype correlations, with interesting preliminary. For example, compared with those without a desmosome gene mutation, individuals with a desmosome gene mutation had earlier-onset AC and were more likely to have ventricular tachycardia.[42] Recent studies have also suggested that for rare desmosome gene mutations (namely, *DSG2* and *DSC2*), the presence of multiple mutations simultaneously may be required to manifest the AC phenotype[43] and may be associated with increased disease severity, namely higher frequency of sudden death.[28]

## CLINICAL PICTURE AND TASK FORCE CRITERIA

Clinically, the patient usually presents with palpitations, due to premature ventricular complexes (PVCs) or nonsustained ventricular tachycardia. Other presentations are sustained ventricular tachycardia, syncope, resuscitated cardiac arrest, right heart failure or late stage biventricular heart failure.[12] Multiple criteria are needed to diagnose AC, as there is no single gold standard criterion sufficiently specific to establish the diagnosis.[41] Even the presence of desmosomal genetic abnormality is not sufficient as there is variable penetrance. However, it is important to note that the recessive form of AC (Naxos disease) presents full penetrance by adolescence, being associated with cutaneous abnormalities consisting of woolly hair and palmoplantar keratoderma.[44] This diagnostic challenge led to the formation of an expert Task Force that in 1994 proposed major and minor criteria to aid in the diagnosis.[45] The report achieved its goal of standardizing diagnostic criteria. With the growing international experience, an updated modified task force criteria (TFC) were published in 2010.[46] The modified criteria include structural alterations observed by echocardiogram, cardiac magnetic resonance imaging and/or angiography. They also include tissue characterization of RV wall, repolarization abnormalities, depolarization abnormalities, arrhythmias, and family history (Table 2). The modified criteria are also based on more quantitative analysis rather than the 1994 TFC qualitative nature.

## ELECTROCARDIOGRAM

The 12-lead electrocardiogram (ECG) is one of the most important tools for the diagnosis, follow-up and SCD risk stratification of AC (Figure 5). Depolarization abnormalities due to activation delay as a result of cellular uncoupling and fibrofatty alteration include the epsilon wave, widening of the QRS complex (>110 msec) in leads $V_1$ to $V_3$ and evidence of late potentials by signal averaged ECG (SAECG). Epsilon wave is a defined as reproducible low amplitude signals between the end of the QRS complex to

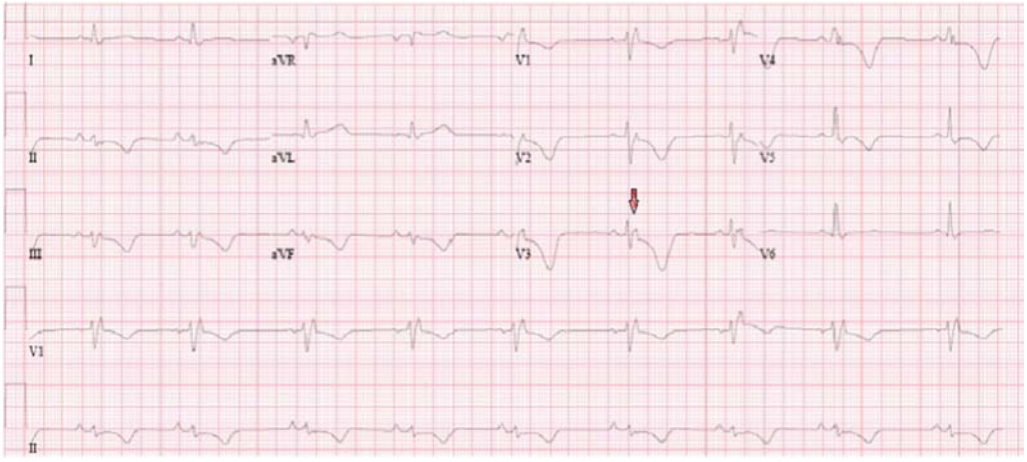


**Figure 5. 12 Lead ECG of arrhythmogenic cardiomyopathy. Note the "epsilon wave" in $V_3$, the right pericardial leads localized QRS prolongation which is mainly due to a terminal activation delay (from nadir of S to the end of QRS complex), and T wave inversion in $V_{1-3}$.**

the onset of the T wave in the right precordial leads ($V_{1-3}$). Although the epsilon wave is very specific for AC, Cox et al, showed that this parameter had a very low sensitivity (10%). Widening of the QRS complex was a criterion in 1994 TFC, but it was deleted in the 2010 TFC due to possible confusion especially in the presence of a right bundle branch block (RBBB). To overcome this confusion, many studies have proposed new ECG markers that focus on delayed RV activation in precordial leads. These include the presence of partial block,[47] delayed S wave upstroke in $V_{1-3} \geq 55$ msec,[48] increased ratio of QRS duration in the right versus the left precordial leads,[49] and a prolonged terminal activation duration $\geq 55$ msec.[50] Right precordial QRS prolongation and QRS dispersion have been significantly associated with an increase of the arrhythmic risk in patients with AC. In an important study, Turrini et al., showed a greater QRS prolongation (125 msec) in V1 to V2/V3 in AC patients with SCD, in comparison with living AC patients (113 msec). They also demonstrated that QRS dispersion of more than 40 msec (between the longest and shortest QRS intervals) was a strong predictor of SCD in AC.[51] Abnormalities in repolarization in AC are represented as inverted T wave. Due to its high sensitivity, inverted T waves in V1-V3 or beyond in the absence of RBBB and in $>12$ year old individuals was upgraded from a minor criterion in the 1994 TFC to a major criterion in the 2010 TFC, for individuals older than 14 years and in absence of complete RBBB.[46] The morphology of recorded ventricular tachycardia (VT) reflects its site of origin. In AC, affected areas in the triangle of dysplasia usually produce a VT with a left bundle branch block morphology and a superior axis, defined from $-30°$ to $-150°$. Because of the variable extension of the disease, multiple VT morphologies are usually recorded in a single patient. Studies showed the mean number of different VT morphologies per patient ranges from 1.8 to 3.8.[52,53]

## ECHOCARDIOGRAPHY

Echocardiography is of paramount importance in the initial evaluation and follow up of AC patients because of its availability, ease of performance and interpretation, cost effectiveness and non invasive advantages (Figure 6).[54] The multidisciplinary Study of Right Ventricular Dysplasia demonstrated that the diagnostic performance of transthoracic echocardiography was superior to MRI with 80% accuracy in affected individuals with AC and 40% accuracy in borderline individuals, compared with 49% and 15% for MRI, respectively.[55,6] RV outflow tract dilatation (in parasternal long axis view $>32$ mm or in parasternal short axis view $>36$ mm) coupled with localized anuerysms (akinesia or dyskinesia) or global dysfunction (fractional area change $<33\%$) is now considered a major criterion for the diagnosis of AC.[46] Other echocardiographic features to assess RV anatomic alteration include the ratio between the RVOT/aorta in parasternal short axis view (abnormal if $>1.2$), longitudinal and transverse RV axes in apical four chamber and subcostal views, visualization of RV apical trabeculation in the subcostal view. Emerging echocardiographic techniques being currently evaluated include 3-dimensional echocardiography,[56] RV free wall myocardial velocity, strain and strain rate by Doppler or speckle tracking (Figure 7).[57,58]

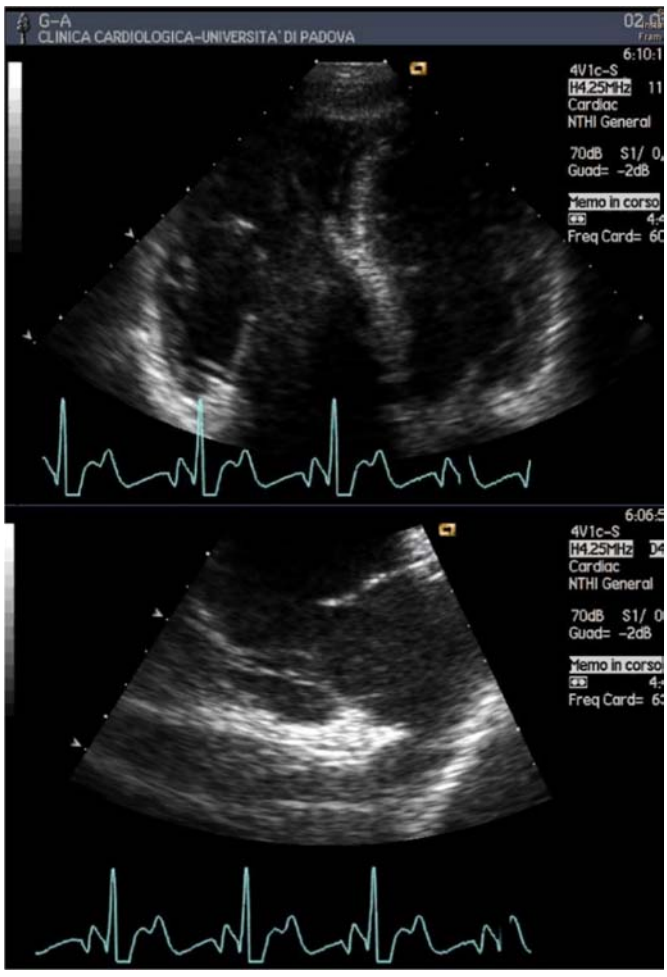


**Figure 6. Echocardiography of a patient with arrhythmic cardiomyopathy. Upper panel shows an apical 4 chamber view with dilated anuerysmal right ventricle. Lower panel shows a modified short axis left paraternal view to visualize the subtricuspid area which shows a localized aneurysm. (Images courtesy of MP Marra, MD, University of Padua, Italy).**

## RIGHT VENTRICULOGRAPHY

RV ventriculography remains an integral imaging modality and reference technique in the diagnosis and evaluation of patients with AC. This technique should be performed in all patients with suspected or definite AC and may be combined with electrophysiological study and/or RV endomyocardial biopsy. The angiographic diagnosis of AC is based on segmental abnormalities rather than diffuse RV enlargement or hypokinesia. Dedicated computer software for the evaluation of RV volume and regional wall motion, have been developed and provide a convenient and reproducible method for quantitative assessment of global and regional RV contraction and relaxation.[59,60]

## MAGNETIC RESONANCE IMAGING

Among the current cardiac magnetic resonance imaging (MRI) applications in cardiomyopathies, the greatest potentials and challenges are in the diagnosis of AC. Routinely used imaging planes are suboptimal for RV evaluation, and the technique of AC imaging involves unconventional imaging planes. Furthermore, the lack of familiarity of the MRI interpreters with RV contraction pattern and the normal epicardial fat distribution pose challenges for accurate and reproducible reporting. Also, it requires a high degree of expertise to accurately differentiate AC from alternative diseases with similar MRI picture -especially late gadolinium enhancement (LGE)- such as myocarditis and sarcoidosis.[61] Finally, over-reliance on the presence of intramyocardial fat has resulted in a high frequency of misdiagnosis of AC.[62] Despite of these limitations, cardiac MRI have emerged as a robust tool to evaluate AC patients (Figure 8). It has the ability to noninvasively provide tissue characterization for

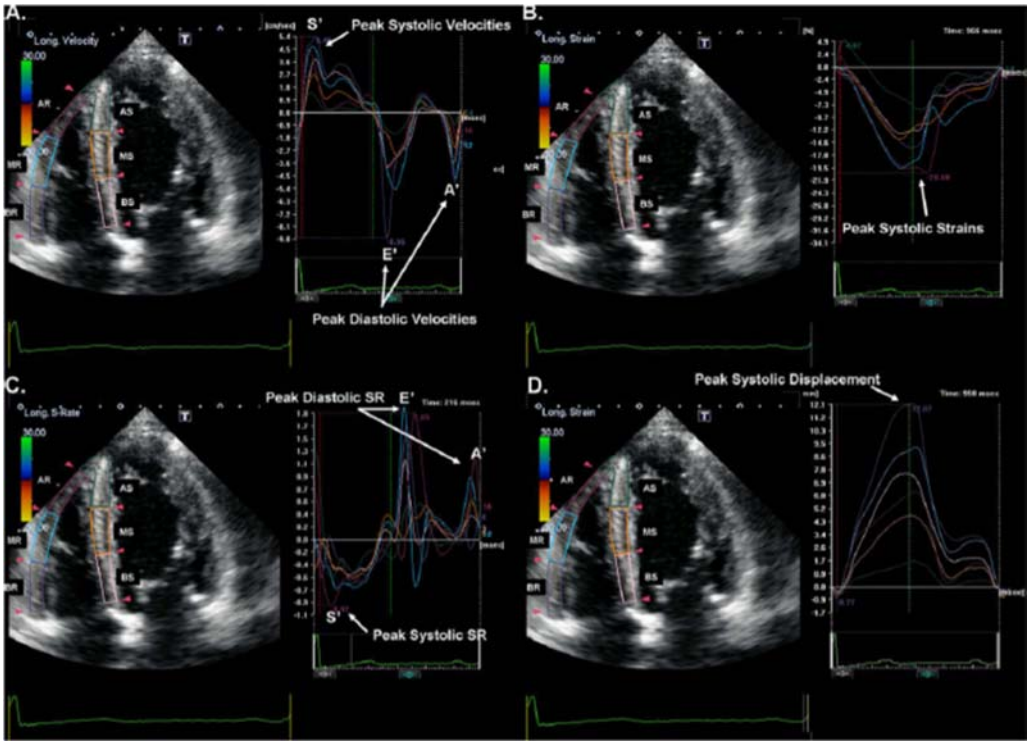


**Figure 7. Apical 4-chamber view with 2D speckle imaging of the LV septum and RV free wall in a normal older patient. The images display longitudinal velocity (A), strain (B), strain rate (SR) (C), and displacement (D) curves. A', Late diastolic waveform; AR, apical right ventricle; AS, apical septum; BR, basal right ventricle; BS, basal septum; E', early diastolic waveform; MR, mid right ventricle; MS, mid septum; S', systolic waveform. Adapted from Horton K, *et al.* Assessment of the right ventricle by echocardiography: a primer for cardiac sonographers. *Journal of the American Society of Echocardiography* 22, 776-92 (2009)**

detection of fat and more importantly fibrosis in the RV, and also the LV. Quantitative data on ventricular volumes, functions, and regional contraction abnormalities are useful in the diagnosis and follow up of patients with AC.[63] MRI studies have also helped in genotype-phenotype correlation of AC; LV involvement is rare in PKP 2 mutation but more common in desmoplakin and plakoglobin mutation carriers.[17,64]

## ELECTROPHYSIOLOGICAL MAPPING AND ABLATION

Three-dimensional electro-anatomic mapping has helped in understanding the substrate and mechanisms underlying VT in AC patients. Electrical activation through normal RV myocardium was defined in patients with no structural heart disease with the use of the CARTO electro-anatomic mapping system and the Navistar catheter (Biosense Webster, Diamond Bar, CA, USA), which has a 4-mm distal tip electrode, and a 1-mm inter-electrode distance. Normal RV endocardium is characterized by bipolar signals displaying 3 or fewer deflections from baseline, with peak-to-peak amplitude greater than 1.5 mV, whereas areas of bipolar voltage less than 0.5 mV correspond to dense scar, i.e., electrovoltage scar (EVS). RV bipolar EVS was demonstrated to correlate with the histopathologic finding of fibrofatty myocardial replacement at endomyocardial biopsy in AC patients.[65,66] Corrado et al demonstrated that electrovoltage mapping enhances the diagnostic specificity of AC by distinguishing between pure genetically-determined AC, which is characteristically associated with EVS involvement, and acquired RV inflammatory cardiomyopathy, mimicking AC but showing a preserved electrogram voltage and a better prognosis.[65,66] Moreover, electrovoltage mapping has been proven to increase diagnostic sensitivity for early/minor form of AC underlying apparently idiopathic RVOT tachycardias, by detecting otherwise concealed segmental RV EVS areas in the RVOT, which are associated with a worse arrhythmic outcome.[66] Finally, EVM has been recently reported to be significantly more sensitive than contrast-enhancement-cardiac magnetic resonance in identify RV scar lesion (Figure 9).[67] In accordance with the pathological findings concerning the progress of the fibrofatty dystrophy from the epicardium towards the endocardium; Garcia et al demonstrated that most patients with AC have a far

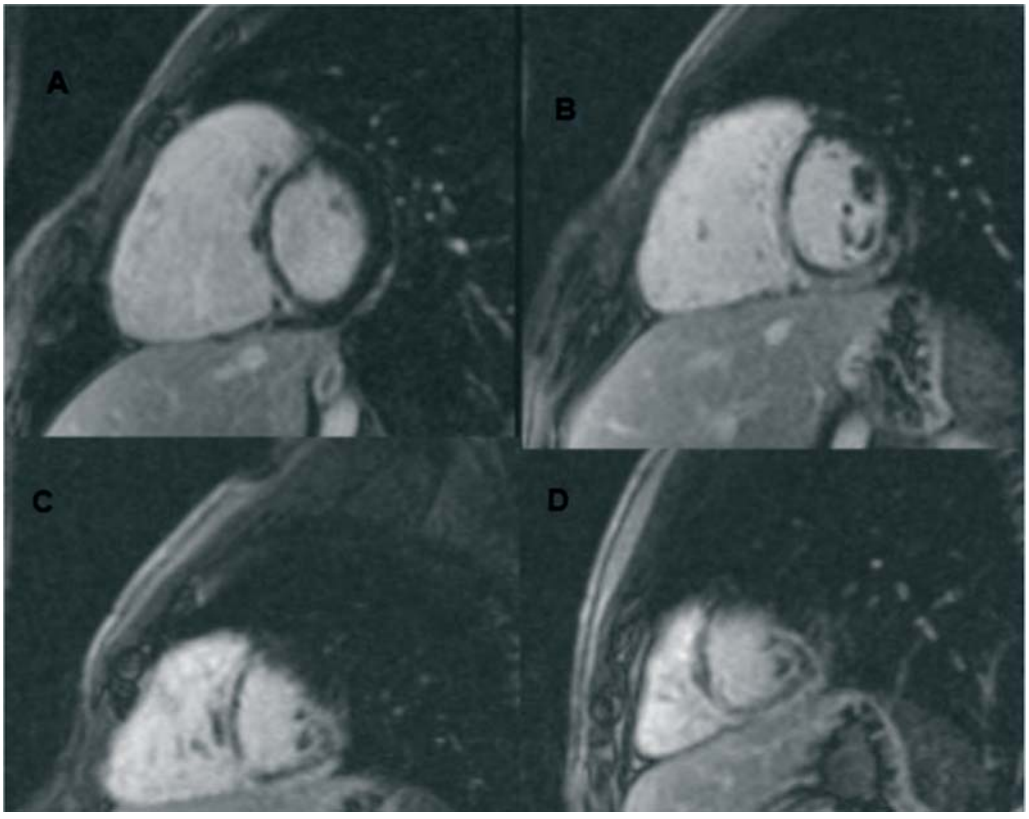


**Figure 8. Cardiac magnetic resonance imaging of a patient with extensive AC. Short axis view from base (upper left) to apex (lower right) demonstrating extensive fibrosis as evidenced by delayed gadolinium enhancement in most of right ventricular wall (only sparing a small infero-septal area), interventricular septum and the epicardium of the left ventricular inferior wall. This patient underwent cardiac transplantation for severe right heart failure. (Images courtesy of MP Marra, MD, University of Padua, Italy)**

more extensive substrate for VT using epicardium mapping than they do on RV endocardium.[68] Due to the disappointing initial results endocardial ablation results,[69] VT ablation as a line of therapy for patients with AC has been considered only in patients with end-stage AC, incessant VT, frequent implantable cardioverter defibrillator (ICD) interventions and intolerable antiarrhythmic drugs side-effects. However, more promising results have been recently published using more aggressive and sophisticated endocardial and epicardial substrate mapping and ablation techniques.[68,70] Yet, those results, being exclusive to very highly experienced centers, may be difficult to reflect in general practice.

## PHARMACOLOGICAL THERAPY

Pharmacological treatment has been another challenging aspect in AC, given the small number of patient study populations and the near lack of randomized clinical trials. One of the largest series of pharmacologic therapy in AC is from Germany, first published in 1992 and updated in 2005 with 191 patients and 608 drug tests.[71,72] Sotalol at a dosage of 320-480 mg/d was the most effective drug resulting in a 68% overall efficacy. Combinations of amiodarone and beta-blockers were also efficacious. Another large study was presented from the North American Registry in 2009.[73] Of 108 patients in this registry, it was concluded that there was no clinically significant benefit in preventing malignant ventricular arrhythmias with beta-blockers. However there was a trend in the reduction in number of shocks in patients with implantable cardioverter defibrillator (ICD) and on a beta-blocker therapy. In opposition to the German registry, sotalol failed to show any clinical benefit, with worse outcomes associated with highest doses of sotalol. A small number (10 patients) were studied for amiodarone, and they showed 75% lower risk of any clinically relevant ventricular arrhythmias compared with all other patients. The mixed results from those two registries lead to the conclusion


**Figure 9. A: Bipolar endomyocardial electrovoltage mapping of a patient with arrhythmogenic cardiomyopathy. Red color represents areas of a low voltage recordings $<$ 0.5 mV indicating a dense scar tissue. B: Cardiac magnetic resonance of the same patient. Extensive fibrotic changes demonstrated by delayed gadolinium enhancement in most of the right ventricular free wall and extending into the interventricular septum (concordant to the electrovoltage mapping findings). (Images courtesy of MP Marra, MD, University of Padua, Italy)**

that there is not sufficient evidence to adequately guide physicians considering pharmacological management of AC.[74]

## IMPLANTABLE CARDIOVERTER DEFIBRILLATOR

There is accumulating evidence that ICD provides life saving protection by effectively terminating ventricular arrhythmias in high-risk patients with AC, coining ICD therapy as the gold standard line of management for those patients. One of the most seminal mutli-center studies of ICD therapy in AC is the DARVIN I study. The study was published in 2003, with a study population of 132 AC patients, 80% of them received ICD implant because of a history of either cardiac arrest or sustained VT (secondary prevention). Over the study period of 39 $\pm$ 25 months, 3 deaths occurred (only one SCD; one for infective endocarditis and one for heart failure), 48% of patients (64 out of 132) had at least one appropriate ICD intervention. Fifty-three of the 64 patients were receiving antiarrhythmic medication at the time of the first appropriate shock. Twelve percent of the patients received inappropriate ICD interventions and 16% had ICD-related complications (Figure 10).[75] This was followed by the mutli-center DARVIN II study which focused on primary ICD prevention in high risk AC patients. The study included 106 patients with AC and no prior VF or VT who received an ICD because of one or more arrhythmic risk factors such as syncope, asymptomatic nonstained VT, familial SCD and inducibility of sustained VT by programmed ventricular stimulation in the electrophysiological laboratory. During a mean follow up of 4.8 years, no death occurred, and 24% of the patients received appropriate ICD interventions and 19% received inappropriate interventions.[76] In a large single center study, Witcher et al., reported 60 AC patients who received ICD therapy and were followed up for a period of 80 $\pm$ 43 months The majority of the cases received their ICD as a secondary prevention. With only 26% of event free follow up in the highest risk group, the study confirmed the improvement of long term prognosis of high risk AC patients who undergo ICD implantation.[77]

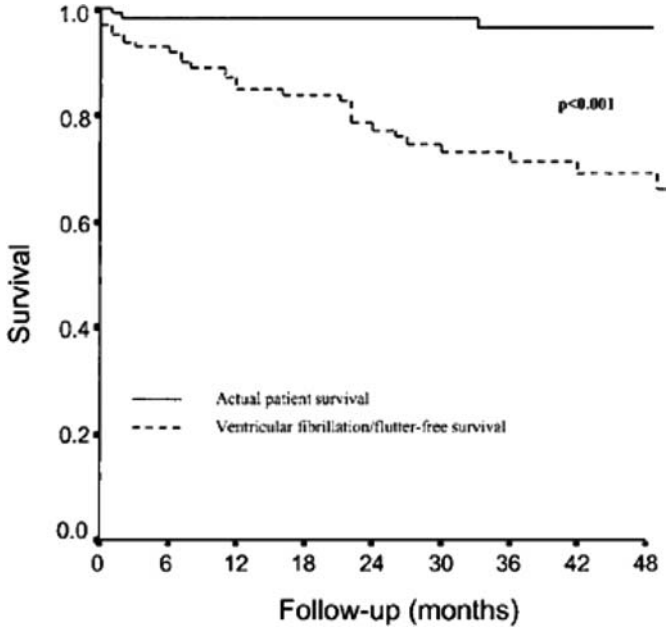


**Figure 10.** DARVIN I Kaplan-Meier analysis of actual patient survival (upper line) compared with survival free of ventricular fibrillation/flutter (lower line) that in all likelihood would have been fatal in the absence of the ICD. The divergence between the lines reflects the estimated mortality reduction by ICD therapy of 24% at 3 years of follow up. Adapted from Corrado, D. *et al.* Implantable cardioverter-defibrillator therapy for prevention of sudden death in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circulation* 108, 3084-91 (2003).

## SPORTS AND PRE-PARTICIPATION SCREENING

The cornerstone in the management of AC as a cause of SCD relies on screening among high-risk population. Corrado et al., have shown that the risk of sudden death from AC has been estimated to be 5.4 times greater during competitive sports than during sedentary activity (Figure 11).[13] This can be

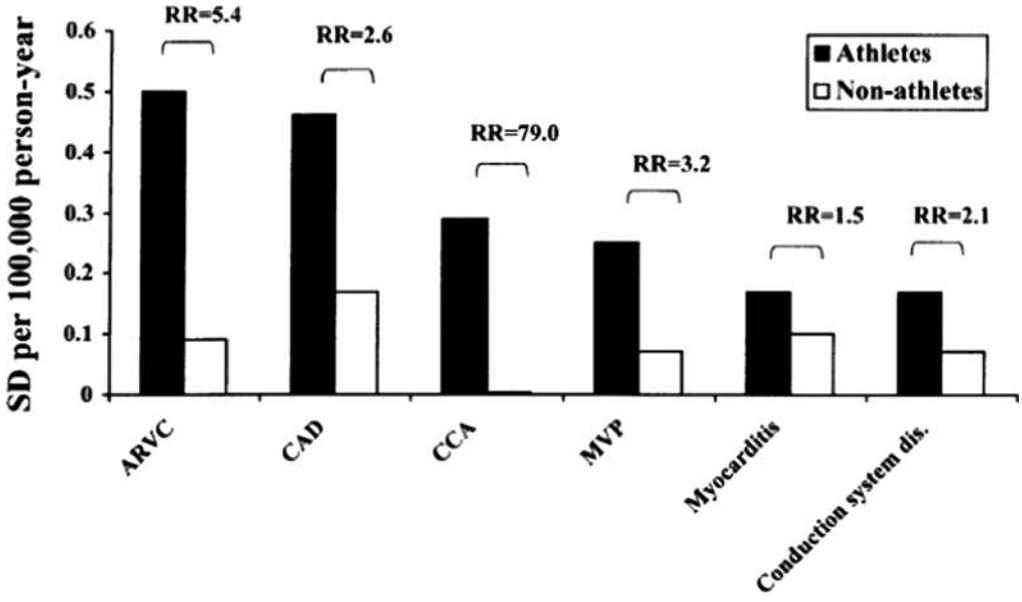


**Figure 11.** Incidence and relative risk (RR) of sudden death (SD) for specific cardiovascular causes among athletes and non-athletes. ARVC: arrhythmogenic right ventricular cardiomyopathy; CAD: coronary artery disease; CCA: congenital coronary artery anomaly; MVP: mitral valve prolapse. Adapted from Corrado, D., Basso, C., Rizzoli, G., Schiavon, M. & Thiene, G. Does sports activity enhance the risk of sudden death in adolescents and young adults? *J Am Coll Cardiol.* 42, 1959-63 (2003).

attributable to the fact that physical exercise acutely increases the RV afterload and causes cavity enlargement, which in turn may elicit ventricular arrhythmias by stretching the diseased RV myocardium. This theory has been confirmed by Kirchof et al., in an experimental study on heterozygous plakoglobin-deficient mice, when compared with wild-type controls, the mutant mice had increased RV volumes, reduced RV function, and more frequent and severe VT of RV origin. Endurance training accelerated the development of RV dysfunction and arrhythmias in the plakoglobin-deficient mice.[78] For more than 30 years, a systemic pre-participation screening for athletes, based on 12-lead ECG, in addition to history and physical examination, has been in practice Italy. A time trend analysis of the incidence of SCD in athletes aged 12 to 35 years in the Veneto region in Italy between 1979 and 2004 has proved compelling evidence of the efficiency of this life saving screening strategy. The annual incidence of SCD in athletes decreased by 89%, from 3.6 per 100,000 during the prescreening period, to 0.4 per 100,000 in the late screening period.[79] This is highly attributable to the efficiency of ECG in detecting HCM and AC as the most common causes of SCD amongst athletes. Moreover, during long-term follow-up, no deaths were recorded in the disqualified athletes with HCM, suggesting that restriction from competition may reduce the risk of SCD.[80]

## CONCLUSION

The evolution of the clinical, investigational, and basic sciences has changed much of our understanding on ARVC shifting it to the wider concept of AC. The scientific community is yet challenged with a long path of research to fully unveil the many faces of this potentially lethal condition.

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