Arrhythmogenic Cardiomyopathy state-of-the-art.

Andrés R Pérez-Riera 1, Raimundo Barbosa-Barros 2, Rodrigo Daminello-Raimundo 1, Luiz C de Abreu 1, Kjell Nikus 3

Affiliations

1. **Laboratorio de Delineamento de Estudos e Escrita Científica, Centro Universitario Saude ABC, Santo Andre, Sao Paulo, Brazil. Universidade Uninove Campus Mauá Disciplina de Clínica Médica..**
2. **Coronary Center of the Hospital de Messejana Dr. Carlos Alberto Studart Gomes, Fortaleza, Ceara, Brazil.**
3. **Heart Center, Tampere University Hospital and Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland.**

Denominations:

ACM: arrhythmogenic cardiomyopathy (the newest designation); **ARVC**: arrhythmogenic right ventricular cardiomyopathy; **ARVD**: arrhythmogenic right ventricular dysplasia; **ARVC/D**: arrhythmogenic right ventricular cardiomyopathy/dysplasia; **LDAC**: Left-dominant arrhythmogenic cardiomyopathy; and **ALVC**: Arrhythmogenic left ventricular cardiomyopathy.

Acronyms used in this presentation

AD: autosomal dominant; **AE:** arrhythmic event; **AF**: atrial fibrillation; **ALVC:** arrhythmogenic left ventricular cardiomyopathy; **AR** autosomal recessive; **BBs**: Beta-Blockers; **BrS**: Brugada syndrome; **BSA**: Body Surface Area; **CA**: cardiac arrest; **CHF**: congestive heart failure; **CMRI**: Cardiovascular Magnetic

Resonance Imaging; **CPVT**: catecholaminergic polymorphic ventricular tachycardia; **CRBBB:** complete right bundle branch block; **CT:** computed tomography; **DCM:** Dilated cardiomyopathy; ε: epsilon; **ECG:** Electrocardiogram; **EAM:** Three-dimensional electroanatomic mapping; **ERS:** Early Repolarization Syndrome; **EMB:** endomyocardial biopsy; **EPS:** electrophysiological study; **HRECG:** high-resolution electrocardiogram; **IRBBB:** incomplete right bundle branch block; **ICD:** implantable cardioverter-defibrillator; **JWS:** J-Wave Syndrome; **LGE:** late gadolinium enhancement; **LBBB:** left bundle branch block; **LPs:** late potentials; **LQTS:** long QT syndrome; **LTVA:** life-threatening ventricular arrhythmia; **LV:** left ventricle/left ventricular; **LVGLS:** Left ventricular global longitudinal strain; **MACE:** Major Adverse Cardiac Events; **MDCT:** multi-dimensional computed tomography; **OMIM:** Online Mendelian Inheritance in Man; **MIM:** *Mendelian Inheritance in Man;* **NCC:** Non-compaction cardiomyopathy; **P/LP:** pathogenic/likely pathogenic variants*;* **NSVT:** non-sustained ventricular tachycardia**; PES:** Programmed Electrical Stimulation; **PVCs:** premature ventricular complexes or premature ventricular contractions; **RCM:** Restrictive cardiomyopathy; **RECD:** Right End Conduction Delay; **RFCA:** Radiofrequency catheter ablation; **RV:** right ventricle/ right ventricular; **RVEF:** Right Ventricular Ejection Fraction; **RVFW:** Right Ventricular Free Wall; **RVH:** right ventricular hypertrophy; **RVOT:** right ventricular outflow tract; **RVOT-VT:** Right ventricular outflow tract ventricular tachycardia; **SAECG:** signal-averaged electrocardiogram; **SCD:** sudden cardiac death; **SHD:** structural heart disease; **SUD:** sudden unexplained death; **TAD:** terminal QRS activation delay; **TAPSE:** tricuspid annular plane systolic excursion; **TFC:** Task Force Criteria; **TTE:** transthoracic echocardiogram / echocardiograph; **TWA:** T-wave alternans; **TWI:**

T-wave inversion; **UCA:** unexplained cardiac arrest; **VA:** ventricular arrhythmia; **VF:** ventricular fibrillation; **VT:** ventricular tachycardia; **VUS:** variant of uncertain significance; **WPW:** Wolff-Parkinson-White.

Introduction

Abstract

ACM is an arrhythmogenic heart muscle disorder not explained ischemic, hypertensive, or valvar disease and non-hypertrophic, progressive predominantly genetically determined, characterized by fibrofatty infiltration that affects the RV (the “dominant -right” variant), the LV (the “dominant -LV “variant ALVC) or both (the “biventricular disease” variant”). Consequently, three main phenotypes are currently recognized. The entity is characterized pathologically by the replacement of myocytes by adipose and fibrous tissue and leads to highly variable presentation even within families. In addition, infiltration of inflammatory cells can be observed in approximately 60-80% of patients[1] is seen with advanced stages of the disease, electrical instability may precede CHF alterations with MACE, syncope and SCD, in young individuals and young athletes.

ACM is mostly hereditary with AD inheritance pattern (up to half of all cases), AR, compound heterozygosity and digenic mutations.

Of 26 reported ACM genes, six had strong evidence, two moderate (*DES* and *PLN*) and classified as definitive for ACM causation (*PKP2*, *DSP*, *DSG2*, *DSC2*, *JUP*, and *TMEM43*) and 18 genes had limited or no evidence. *RYR2* was refuted as an ACM gene since clinical data and model systems exhibited a CPVT phenotype. In ClinVar, only 5 pathogenic/likely

pathogenic variants (1.1%) in limited evidence genes had been reported in ACM cases in contrast to 450 desmosome gene variants (97.4%).

Genetic screening is critical in identifying familial mutations, but finds a pathogenic mutation in ≈50% of cases. Some critical genotype-phenotype correlations do exist and may help guide risk stratification and give clues to disease progression. Diagnosis can be challenging due to variable pathophysiology and clinical expressivity continuously in evolution and incomplete penetrance. Expressivity refers to the influence of an expressed gene in individuals. A variable expressivity pertains to the consistency of the gene's influence on the individual. It occurs when a phenotype is expressed but to a different degree among individuals with the same genotype.

Up to 60% of patients with ACM have pathogenic or likely pathogenic (P/LP) variants[2] in genes encoding the cardiac desmosome (*PKP2*, *DSP*, *DSC2*, *DSG2*, and *JUP*).[3]

Pathogenic variants in extra-desmosomal ACM-associated genes including *CTNNA3*,[4] *PLN*,[5] *TMEM43*,[6] *SCN5A*,[7] *CDH2*,[8] and *DES*[9] which are less prevalent.

Differential diagnostic frequently is a challenging, especially in differentiating ACM from other conditions such as fatty infiltration of the RV free wall and/or presence of focal intra-myocardial fat, RVOT tachycardia or idiopathic VT arising from the RVOT Idiopathic infundibular PVC/VT, athlete's heart, myocarditis, sarcoidosis, BrS, Uhl’s anomaly, Ebstein’s anomaly, interatrial septal defect, anomalous pulmonary venous return, tricuspid regurgitation, and inferior myocardial infarct with RV compromise.

Therapeutic strategies include restriction from high endurance and competitive sports, BBs, antiarrhythmic, CHF treatment, implantable ICDs and combined endocardial/epicardial catheter ablation. Ablation has emerged as the treatment of choice for recurrent MACE in ACM.

This review outlines the epidemiologic dates, pathogenesis, diagnosis, differential diagnosis, and treatment of ACM.

Keywords: ACM, ARVC; ARVD; epidemiology; genetics; electrocardiology; diagnosis; differential diagnosis; treatment.

ACM in the context of cardiomyopathies: Main historical chronologic advances

Cardiomyopathies: From the Greek roots: "cardio-" heart + "mys", muscle + "pathos", disease = disease (of the) heart muscle.

XVIII century in **1728**, the Italian clinician and anatomist Giovanni Maria Lancisi (Latin name: Johannes Maria Lancisius) born Oct. 26, 1654, Rome, Papal States Italy - died Jan. 20, 1720, Rome), considered the first modern hygienist. His landmark *De Motu Cordis et Aneurysmatibus* was the results of his observations were posthumously published. Figure x. The work was edited by Pietro Assalti (latinized as Petrus Assaltus) who also conducted the autopsy of Lancisi and identified his death as being caused by a duodenal infarction.[10] Lancisi reported a four-generation family affected by palpitations CHF, and SCD, in which autopsy revealed dilatation and aneurysms of the RV.[11] In this posthumous work,[1] he discussed the various causes of cardiomegaly, aneurysms of syphilitic origin, markedly contributed to knowledge of cardiac

pathology. Assalti collected and edited Lancisi's work as *Opera omnia in duos tomos distributa*, 2 vols. (Geneva, 1718). The year before, his annotations to Michele Mercati's *Metallotheca* (Rome, 1717) had appeared. He was also responsible for the preface to Lancisi's *De motu cordis et aneurysmatibus* (Rome, 1728).

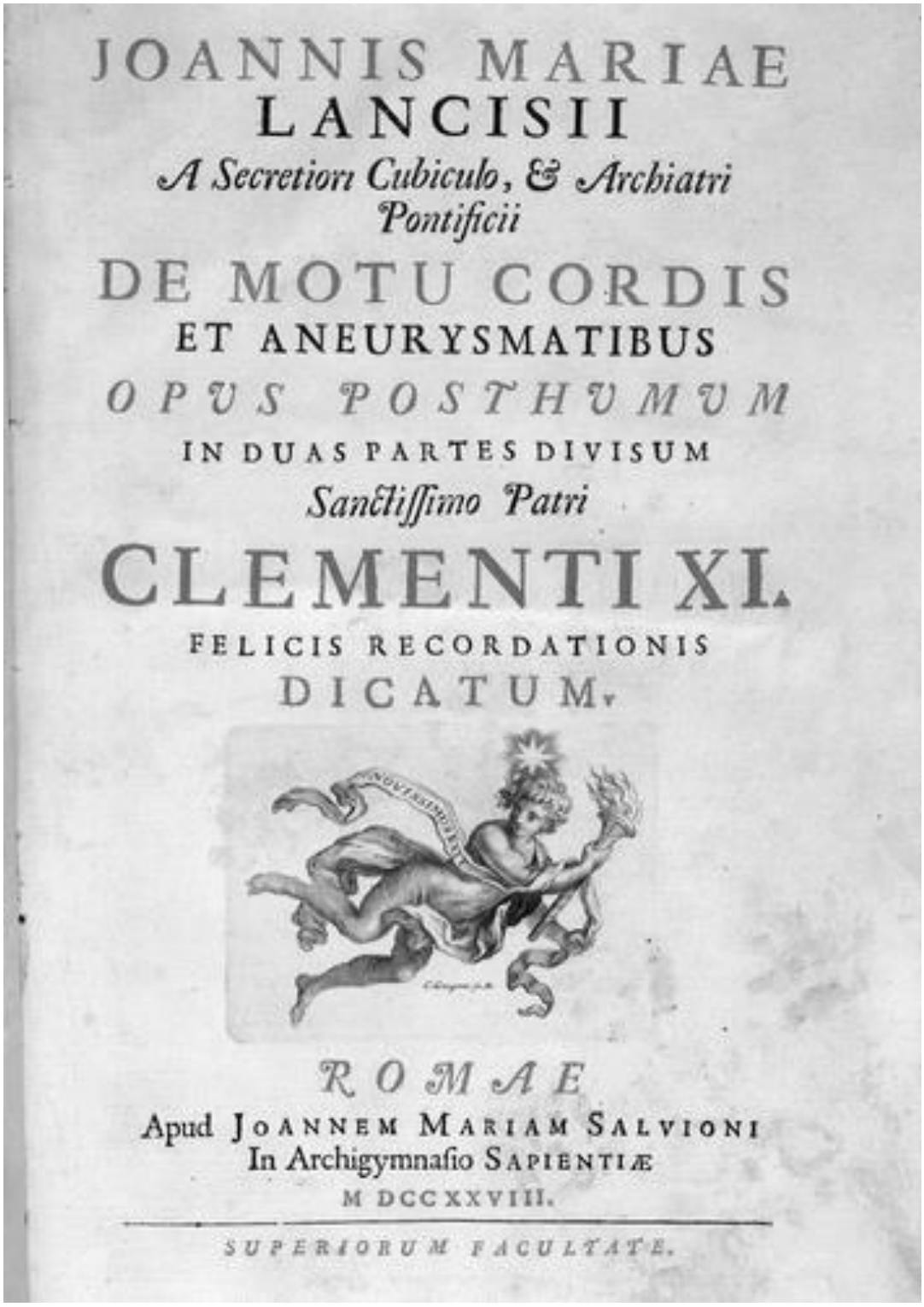

JOANNIS MARIAE
LANCISII
A Secretiori Cubiculo, & Archiatri Pontificii
DE MOTU CORDIS
ET ANEURYSMATIBUS
OPUS POSTHUMUM
IN DUAS PARTES DIVISUM
Sanctissimo Patri
CLEMENTI XI.
FELICIS RECORDATIONIS
DICATUM.
ROMAE
Apud JOANNEM MARIAM SALVIONI
In Archigymnasio SAPIENTIÆ
M DCCXXVIII.
SUPERIORUM FACULTATE.

Figure x. Frontis piece of *De Motu Cordis et Aneurysmatibus* (1728).[12]

In the last years of his life, Lancisi again focused his attention on the study of diseases of the heart and the great vessels, particularly. In those years, his

contribution was not limited only to scientific aspects; he also tried to reform the education of future generations of physicians. At that time, medical students had mainly a theoretical and philosophical education at the university, without direct contact with patients. For this reason, after completing their studies the young physicians had to carry out a period of practical apprenticeship in a hospital, as did the young Lancisi. On the other hand, in the hospitals theoretical notions were lacking and the medical practice was mainly empirical. In his writing *De Recta Medicorum Studiorum Ratione* (1715) Lancisi proposed a modern medical training model, based on the two pillars “learning in the hospital” and “learning in the library”.[13] On one hand, the student was to attend visits to the sick, and on the other hand, he was to deal with the new philosophy of nature in the library. The aim he pursued was to bridge the gap between theory and practice. In the early years as an apprentice at the Hospital of the Holy Spirit, Lancisi had suffered the lack of medical texts at the disposal of the hospital. Moreover, he reported that moments of theoretical discussion were absent in the hospital, whereas on the other hand there was no practical training during studies at the University. For this reason, on 25 April 1715 Lancisi founded the Accademia Lancisiana within the Hospital of the Holy Spirit. This was an association of medical scholars with the aim of encouraging the discussion and sharing of knowledge of medicine and surgery within the hospital. Lancisi donated his wide collection of medical treatises to the Academy, thus constituting the first nucleus of the Bibliotheca Lancisiana. The Library was created as a place for education of physicians and surgeons of the Hospital of the Holy Spirit, so they could complete their practical formation with a strong theoretical preparation. Lancisi wanted to offer young physicians and surgeons a medical education with a broad selection of medical

books, creating “a place where professors and physicians can gather”.[14] Today, the Library, part of the hospital, holds ~23,000 volumes and 300 published and unpublished manuscripts, Lancisi was a pioneer in the study of cardiovascular pathophysiology in a period of development of “cardiocentric” theory, which revalued the role of the heart as the center of the human body and the source of life.[15] Until the 1700s, physicians maintained the notion derived from Hippocratic writings that the heart could not be affected by diseases (*cor aegrotari non potest*). Lancisi was the first scholar to challenge this theory and to study the pathophysiology of the cardiovascular diseases. The publication of his treatise *De Subitaneis Mortibus* (1707) may be considered “the birth-year of Modern Cardiology”.[16]

Lancisi graduated in medicine from the University of Rome at age 18. He was appointed physician to Pope Innocent XI in 1688 and subsequently was physician to Popes Innocent XII and Clement XI. Lancisi’s monographs on influenza, cattle plague (rinderpest), and malaria revealed his gifts as an epidemiologist. In his book *De noxiis paludum effluviis* (1717; “On the Noxious Effluvia of Marshes”) he related the prevalence of malaria in swampy districts to the presence of mosquitoes and recommended drainage of the swamps to prevent the disease. He wrote the classic monograph *De subitaneis mortibus* (1707; “On Sudden Death”) at the request of Clement XI to explain an increase in the number of sudden deaths in Rome. Lancisi attributed sudden death to such causes as cerebral hemorrhage, cardiac hypertrophy and dilatation, and vegetations on the heart valves. This treatise and *De motu cordis et aneurysmatibus* (1728; “On the Motion of the Heart and on Aneurysms”), in which he discussed the various

causes of heart enlargement and was the first to describe aneurysms of syphilitic origin, markedly contributed to knowledge of cardiac pathology.

In **1869** Henri Liouville described the first case of HCM Liouville in the Gazette Medecine Paris. He described the obstructive HCM at autopsy: “The LV is enlarged and very thick with concentric LVH. When I insert my index finger from the LVOT toward the aortic root, my finger becomes tightly pinched in the myocardium, 1 cm below the aortic valve. When I try to insert my thumb backward through the aortic valve toward the LV, it cannot reach my index finger that I have inserted from the opposite direction. This is due to the obstruction that is caused by the myocardial thickening that is situated below the level of the aortic valve. Eight decades before LV pressure could be measured, French clinician–pathologist Liouville accurately described the key feature of this condition - ventricular hypertrophy - and deduced that it caused intraventricular obstruction![17]

In **1891,** Krehl described idiopathic diseases of the cardiac muscle.[18]

In **1899** the concept of isolated, non-ischemic disease of the myocardium is born: Acute Interstitial Myocarditis. Autopsy showed acute myocarditis, unrelated to acute rheumatic fever, syphilis, tuberculosis, arteriosclerosis, or septicemia.[19]

In **1901** Louis Josserand and Galvardin (1875, Lyon – 2 December 1957, Lyon) introduced the term primary myocardial disease.[18, 20]

In 1905 The parchment heart or Uhl anomaly, was mentioned by Osler in his ‘The principles and practice of Medicine’

In **1907** Dr. A. Schmincke, a German pathologist, described two hearts with LVH; both came from women in their mid-fifties.[21]

In **1949** there were reports of families with unexplained cardiomegaly.[22]

Uhl in **1952** described the absence of the RV myocardium in an infant who died of CHF, most probably a congenital malformation.

In **1956**, Blankerhorn and Gall Search of 3,141 autopsies found 108 examples of myocardial disease of which 77 were inflammatory (non-rheumatic) and 31 non-inflammatory but degenerative and not due to sclerosis or hypertension. These are designated myocardosis. Myocarditis was associated with infections in a manner often described; myocardosis was associated with a variety of noninfectious disorders. Clinical records also the authors studied to find what part such lesions played in causing death and how such myocardial lesions could be diagnosed with more certainty.[23]

In 1**957** noncoronary cardiomyopathies or idiopathic myocardial disease is described, frequently with a familial background. The nomenclature cardiomyopathy was used by Wallace Brigden to refer to uncommon non-coronary myocardial diseases of unknown etiology. The isolated myocardial diseases are usually distinguishable from the more common forms of cardiomegaly with CHF. Important points are: the insidious development of symptoms from biventricular HF; the high venous pressure and the characteristic wave of the venous pulse; triple rhythm in the absence of murmurs; the diffuse nature of the ECG changes; and, on radiography, the clear silhouette of a relatively immobile heart. Cardiomyopathies may be caused by any of the known disease processes which affect other systems in man. Every case of suspected cardiomyopathy demands a detailed history, repeated examination, and elaborate investigation. By such means the proportion of cases termed " idiopathic " should be diminished, and the whole picture of these interesting conditions made clearer.[24]

In **1960** Dalla Volta from Padua related for the first time the hemodynamic of ACM called “auricularization of the RV pressure”

In **1961,** Goodwin described congestive cardiomyopathy characterized by dilation and CHF from a different and mostly unknown etiology. In other words, they developed a classification according to three major clinical presentations: (1) CHF and atrioventricular valvular incompetence, usually simulating CHD currently called DCM; (2) a presentation simulating constrictive pericarditis currently called RCM; and (3) a presentation simulating obstruction to one or other inflow or outflow tract, currently called HCM, the commonest being the LVOT.[25]

In **1968,** the term cardiomyopathy was used by the World Health Organization for myocardial disease of unknown etiology, characterized by CHF with cardiomegaly. A common name, "idiopathic cardiomegaly", was therefore suggested for future use.[26]

Oakley in 1971 described cardiomyopathy as a heart muscle disorder of unknown cause.[27] In the same year, John Goodwin suggested classifying primary cardiomyopathy, abandoning the term secondary cardiomyopathy, and classifying cardiomyopathy according to the underlying disease; however, this was complex and did not include all cases.

In **1972,** Goodwin and Oakley reported cardiomyopathy as a myocardial disease of unknown cause and classified it based on functional pathology findings as

1. **Congestive**
2. **Hypertrophic** (with or without obstruction) characterized by impaired diastolic compliance.

3. **Obliterated** cardiomyopathy; however, the last should be classified as a specific heart muscle disease because of its rarity. mainly primary amyloid, and occasionally leukaemic infiltration or polyarthritis nodosa.[28]

In **1980** a task force of the World Health Organization (WHO), chaired by John Goodwin, presented the first classification of the cardiomyopathies “heart muscle diseases of unknown cause” which was based on the predominant structural and hemodynamic phenotype.[29], reflecting a general lack of etiologic factors which may cause CHF.

In **1982**, Goodwin stated that ‘‘A classification serves to bridge the gap between ignorance and knowledge,’’ showing the challenges of cardiomyopathy classification at that time. The World Health Organization (WHO)/International Society and Federation of Cardiology (ISFC) Task Force defined cardiomyopathy as heart muscle diseases of unknown etiology, reflecting the poor knowledge of cardiac diseases at that time, and proposed a new cardiomyopathy classification; cardiomyopathies were classified as DCM, HCM, and RCM, which should be differentiated from unclassified cardiomyopathy that did not fit into these groups. Unclassified cardiomyopathy included latent cardiomyopathy with initial cardiac abnormalities and specific heart muscle diseases of known cause or associated with systemic diseases (4). Additionally, to systemic, pulmonary hypertension, CAD, valvulopathies, and congenital cardiac diseases were excluded.

In **1996,** the WHO/ISFC Task Force published a new classification based on current knowledge of the dominant pathophysiology, etiology, and/or pathogenesis of cardiac diseases. Cardiomyopathy was defined as myocardial disease associated with cardiac dysfunction, and divided into dilated,

hypertrophic, and restrictive. For the first time, ARVC and RCM were included; unclassified cardiomyopathies that did not fit into these groups, such as noncompacted myocardium, mito chondrial, fibroelastosis, and systolic dysfunction with minimal dilation, were also included in this classification. Specific cardiomyopathies, previously known by particular heart muscle diseases, that are associated with specific conditions or systemic disorders were included. Ischemic, valvular, and hypertensive cardiomyopathy were included in the group of specific cardiomyopathies, leading to confusion about the meaning of myocardial diseases.

In **2006** is published the Classification and definition of the cardiomyopathies following 2006 American Heart Association Scientific Statement.[30]

In **2008** occurs the Classification of the cardiomyopathies following the position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases.[31]

American Heart Association classification for cardiomyopathies

Primary Cardiomyopathies	Genetic	HCM/ARVC/LVNC/Conduction defects/Mitochondrial myopathies/ion channel disorders
	Mixed	DCM/RCM
	Acquired	Inflammatory/ Takotsubo/ Peripartum/ Tachycardia induced/Infants of IDDM mothers
Secondary Cardiomyopathies	Infiltrative Storage Toxicity Endomyocardial Inflammatory Endocrine	Amyloidosis, Gauchers, Hurler's, Hunter's Fabry's, Glycogen storage disease, Niemann-Pick disease, haemochromatosis

	Cardiofacial Neuromuscular Nutritional Autoimmune	Drugs, heavy metals, Alcoholic cardiomyopathy, Anthracyclines, cyclophosphamide EMF, Loeffler's endocarditis Sarcoidosis Diabetes, hyperthyroidism, hypothyroidism, hyperparathyroidism Noonan's, lentiginosis Friedreich's ataxia, Duchenne-Becker muscular dystrophy, myotonic dystrophy Beriberi, scurvy, selenium SLE, dermatomyositis, scleroderma

ARVC: Arrhythmogenic right ventricular cardiomyopathy/dysplasia; DCM: Dilated cardiomyopathy; HCM: Hypertrophic cardiomyopathy; LVNC: Left ventricular non-compaction; EMF: Endomyocardial fibrosis.

In **2013** is postulate the 2013 MOGE(S) classification for a phenotype-genotype nomenclature of cardiomyopathy: endorsed by the World Heart Federation.[32]

ACM Epidemiology

The estimated prevalence of ACM in the general population ranges from 1 in 1,000 to 1 in 5,000. Peters refers as 1:1,000 to 1:1,250.[33] It is reported to be 1:2,000 in some European countries, such as Germany and Italy.[34] In Italy, ACM is the leading cause of death in young athletes, though this is not registered in other countries, such as the United States or Australia.[35]

Campuzano et al[36] reviewed the genetics of ACM, noting that in 35 to 40% of patients no causal mutation had been identified. They stated that incomplete penetrance and variable expressivity are hallmarks of ACM, making it difficult for clinicians to evaluate the risk of developing the disease.

The mean age at diagnosis is 31 years (±13; range: 4-64 years).

Sex-based differences in the incidence are conflicting. Italian studies report that it is more common in males with an approximate ratio of 3:1,[37] on the other hand the United States and the Dutch ACM cohorts report similar incidence between males and females.[3, 38]

In the North American ACM Registry, they found similar frequency of “affected” and “borderline” subjects between men and women. Sex-related differences were observed in baseline ECG (TWIs in V2 are more common in women), abnormal SAECG, Holter-recorded ventricular arrhythmias, and VT inducibility are more frequent in men showed a trend toward greater risk of fast VT than women.[39]

Athletes account for up to 11% of all cases of SCD in Italy (22% of SCD in athletes). It is rarely diagnosed in the United States, possibly due to under diagnosis.[40]

ACM can be inherited as an AD disease with reduced penetrance and variable expression; AR inheritance pattern is also described (Naxos disease, Carbajal syndrome). 12 genes have been linked to ACM, encoding several components of the cardiac desmosome. Dysfunctional desmosomes resulting in defective cell adhesion proteins (such as plakophilin-2, desmocollin 2, desmoglein-2,[41] desmoplakin, and plakoglobin), consequently causing loss of electrical coupling between cardiac myocytes, leading to myocyte cell death, fibrofatty replacement, infiltration of inflammatory cells can be observed in approximately 60-80% of patients causing arrhythmias.[1]

Cardiomyopathies

Classification and definition of the cardiomyopathies following 2006 American Heart Association Scientific Statement

Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electric dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders. The cardiomyopathies affect only the heart (primary) or are associated with systemic diseases.:

I) **Primary:** The term primary is used to describe diseases in which the heart is the sole or predominantly involved organ

   a) Genetic: HCM, ACM, LVNC; Channelopathies characterized by subtle or non-macroscopic SHD: LQTS, SQTS, CPVT, BrS, ERS, JWS.

   b) Mixed: DCM, RCM

   c) Non-genetic or acquired: (inflammatory myocarditis, peripartum, stress cardiomyopathy “broken heart syndrome”, stress- provoked or Tako-tsubo cardiomyopathy)

II) **Mixed:** DCM, RCM (Non-hypertrophied and Non dilated.)

III) **Secondary or specific cardiomyopathies:** forming part of systemic diseases. Secondary describe diseases in which myocardial dysfunction is part of a systemic disorder such as Infiltrative (amyloidosis and Gaucher disease), Storage (haemochromatosis and Fabry's disease), Toxicity (drugs, alcohol, heavy metals, and chemicals/chemotherapy), Inflammatory (sarcoidosis) endocrine (diabetes mellitus; thyroid disorders;

hyperparathyroidism), cardiofacial (Noonan syndrome, lentiginosis) neuromuscular/neurological, nutritional deficiencies, and autoimmune and collagen disorders[30] (Figure 1).

Figure 2 shows an outline of a normal heart and Figure 3 in DCM, HCM, RCM, and ARVC/D.

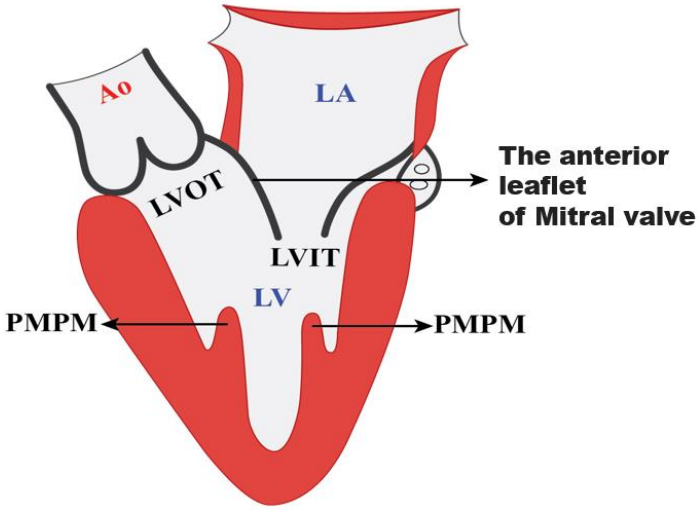
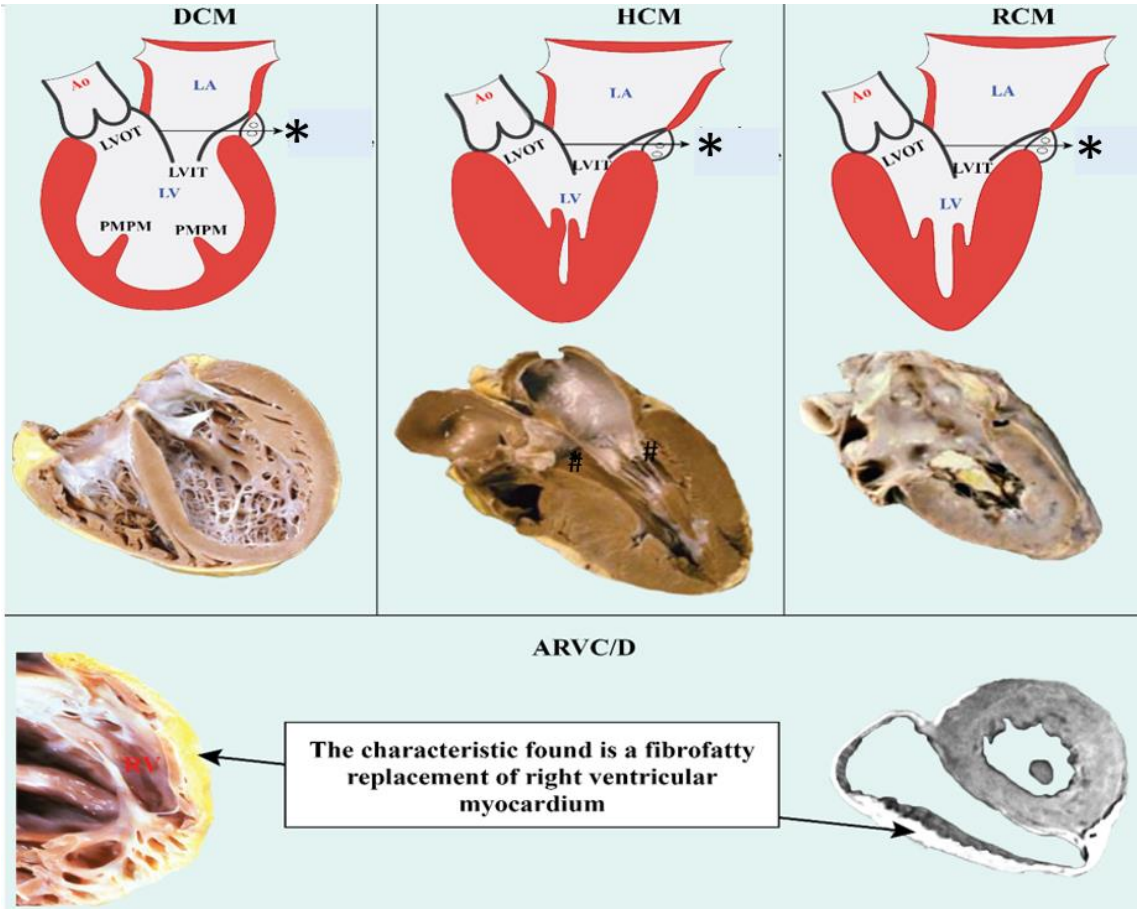


Figure 2. Normal heart. Ao: Aorta; LA: Left Atrium; LV: Left Ventricle; LVIT: Left Ventricular Inflow Tract; LVOT: Left Ventricular Outflow Tract; PMPM: Posteromedial Papillary Muscle. *****The anterior leaflet of Mitral Valve.



Observation

- **VI) Non-compaction cardiomyopathy** (NCC)
- **VII) Channelopathies:** subtle or non-macroscopic SHD.

Figure 3. Illustration of DCM, HCM, RCM, and ARVC/D. Ao: Aorta; LA: Left Atrium; LV: Left Ventricle; LVIT: Left Ventricular Inflow Tract; LVOT: Left Ventricular Outflow Tract; PMPM: Posteromedial Papillary Muscle.[42] The anterior leaflet of Mitral Valve*****

II 2008 Classification of the cardiomyopathies following the position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases.[31] This position paper proposes the previous classification of cardiomyopathies that is designed to provide a valid tool for routine clinical practice. Specific features include:

I. A classification based on groupings of specific morphological and functional phenotypes (rather than putative pathophysiological mechanisms, which may be more suited to research purposes than to everyday practice).

II. Further sub-classification into familial and non-familial forms so as to raise awareness of genetic determinants of cardiomyopathies and to orient diagnostic tests (including the search for specific mutations, when appropriate).

III. Abandonment of the distinction between primary and secondary cardiomyopathies.

IV. A move away from the predominantly exclusion-based diagnostic work-up towards a positive, logical search for diagnostic indicators. The aim of these proposals is to help clinicians look beyond generic diagnostic labels in order to reach more specific diagnoses that may be useful for tailored clinical management of patients and their families.

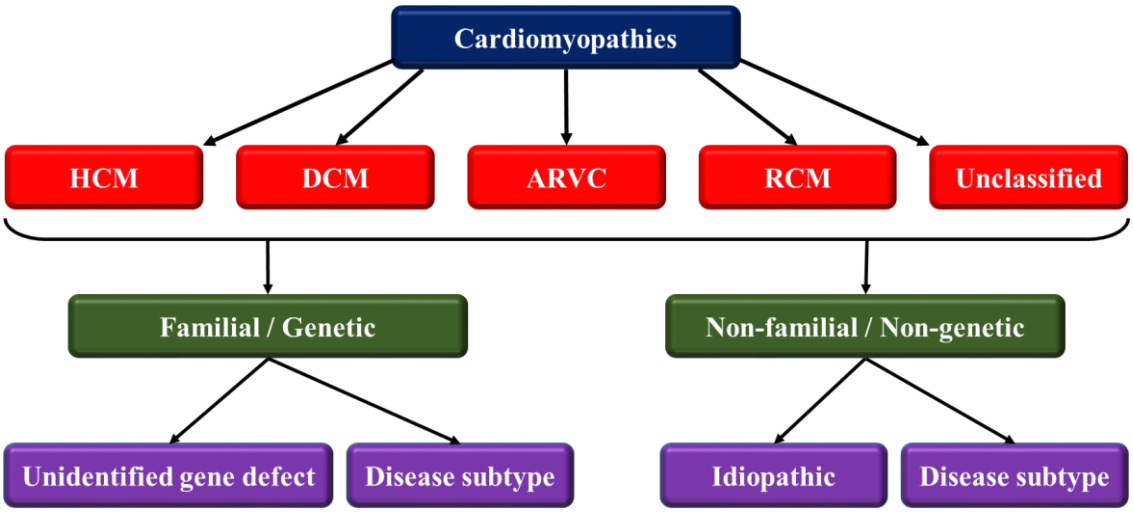


Figure. Summary of proposed classification system. ARVC: arrhythmogenic right ventricular cardiomyopathy; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; RCM: restrictive cardiomyopathy.

Classification of cardiomyopathies

I. **HCM:**

A) Familial: Familial, unknown gene, sarcomeric protein mutations β myosin heavy chain Cardiac myosin binding protein C Cardiac troponin I Troponin-T a-tropomyosin Essential myosin light chain Regulatory myosin light chain Cardiac actin a-myosin heavy chain Titin Troponin C Muscle LIM protein Glycogen storage disease (e.g. Pompe; PRKAG2, Forbes', Danon) Lysosomal storage diseases (e.g. Anderson–Fabry, Hurler's) Disorders of fatty acid metabolism. Carnitine deficiency, Phosphorylase B kinase deficiency Mitochondrial cytopathies, Syndromic HCM: Noonan's syndrome LEOPARD syndrome Friedreich's ataxia Beckwith–Wiedermann syndrome Swyer's syndrome Other Phospholamban pro. Phosphorylase B kinase deficiency Mitochondrial cytopathies Syndromic HCM Noonan's syndrome LEOPARD syndrome Friedreich's ataxia Beckwith–Wiedermann syndrome Swyer's syndrome Other Phospholamban pro

B) Non-familial: Obesity infants of diabetic mothers, athletic training, amyloid (AL/prealbumin).

II. DCM:

A) Familial: Familial, unknown gene Sarcomeric protein mutations (see HCM) Z-band Muscle LIM protein TCAP Cytoskeletal Genes Dystrophin Desmin Metavinculin Sarcoglycan complex CRYAB Epicardin Nuclear

membrane Lamin A/C Emerin Mildly dilated CM Intercalated disc protein mutations (see ARVC) Mitochondrial cytopathy.

B) Non-familial: Myocarditis (infective/toxic/ immune), Kawasaki disease, eosinophilic (Churg Strauss syndrome), viral persistence, drugs, pregnancy, endocrine nutritional - thiamine, carnitine, selenium, hypophosphataemia, hypocalcaemia, alcohol tachycardiomyopathy.

III. ARVC

A) Familial: Familial, unknown gene

- *Desmosomal:* Mutations in the intercalated disc protein of sarcomere: Plakophilin-2 (PKP-2), Desmoplakin (DSP), Desmoglein-2 (DSG-2), Desmocollin-2 (DSC2), Plakoglobin (JUP).
- *Non-desmosomal:* Transmembrane protein 43, transforming growth factor-β3 (TGFβ3).

B) Non-familial: Inflammation?

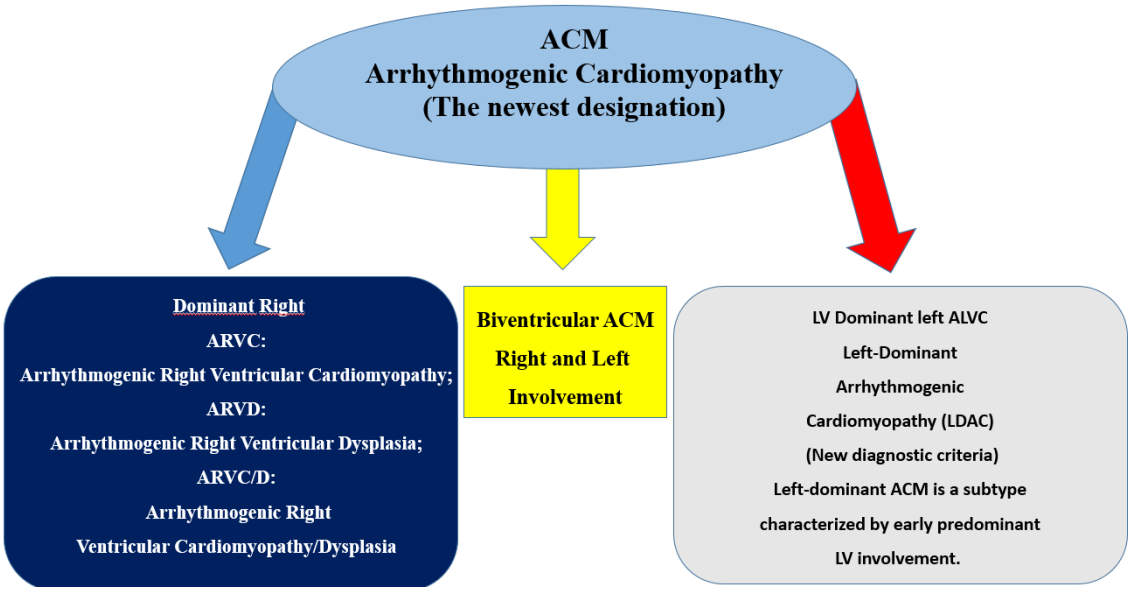
Currently the appropriate denomination for ARVC is ACM which has three main patterns:

I) Dominant right or arrhythmogenic right ventricular cardiomyopathy.

II) Biventricular or right and left involvement.

III) Left Ventricular Dominant Cardiomyopathy (LDAC).

Figure



IV) Restrictive Cardiomyopathy (RCM)

A) Familial: Familial, unknown gene Sarcomeric protein mutations Troponin I (RCM þ/2 HCM) Essential light chain of myosin Familial Amyloidosis Transthyretin (RCM +neuropathy), Apolipoprotein (RCM + nephropathy) Desminopathy, Pseuxanthoma elasticum, Haemochromatosis, Anderson–Fabry disease, Glycogen storage disease**.**

B) Non-familial: Amyloid (AL/prealbumin) Scleroderma, Endomyocardial fibrosis Hypereosinophilic syndrome, Idiopathic Chromosomal Cause Drugs (serotonin, methysergide, ergotamine, mercurial agents, busulfan), Carcinoid heart disease, Metastatic cancers, Radiation, Drugs (anthracyclines).

V) Unclassified

A. **Familial:** Left ventricular non-compaction, Barth syndrome, Lamin A/C ZASP a-dystrobrevin.

B. **Non-familial:** Takotsubo cardiomyopathy.

The 2013 MOGE(S) classification for a phenotype-genotype nomenclature of cardiomyopathy: endorsed by the World Heart Federation. Arbustini et al. proposed classification,[32] similar to the TNM (tumor, node, metastasis) staging system for cancer, known as **MOGE(S),** where

- **M:** Morpho-functional phenotype: DCM, HCM, RCM, ARVC, LVNC and overlapping, more complex combinations, nonspecific phenotype, information not available and unaffected
- **O:** Organ/system involvement, muscle, skeletal, nervous, cutaneous, hair, eye, auditory, kidney, gastrointestinal, skeletal or absence of organ/ system involvement, e.g., in family members who are healthy mutation carriers; the mutation is specified in e and inheritance in:
- **G:** Genetic or familial inheritance pattern,
- **E:** Etiology and functional status
- (**S**) Stage ACC/AHA Stage, NYHA Functional Class using the American College of Cardiology (ACC)/AHA (A to D) and the New York Heart Association functional classes (I to IV).

The main advantage of this classification is the global evaluation to improve diagnosis, treatment, and outcomes of cardiomyopathy patients and family; additionally, it facilitates research through a multicenter classification. After genetic evaluation of an index case, a family screening is mandatory to detect family members who may be healthy carriers of the mutation and could develop the disease in the future; they may then be advised to avoid competitive sports or be treated early before cardiovascular deterioration.

Limitations to MOGE(S) classification

The non-inclusion of

1) Tachycardiomyopathy,
2) Cardiomyopathy associated with endocrine diseases,
3) Peripartum cardiomyopathy.
4) Early stages of myocardial disease and the dynamic evaluation of phenotypes are not embraced; it does not address the risk of SCD which is common in these diseases, acute CHF, that impact the treatment and prognosis of these patients.
5) Chronic Chagasic Cardiomyopathy, which is a chronic inflammatory entity with specific and severe clinical manifestations, endemic in Latin America and with increasing rates in the United States and Europe due to immigration.
6) Covid-19 pandemic could cause myocardial damage, and the inclusion of this disease in the current classification is challenging.

ACM genetic background

The genetic basis of ACM is complex and not fully understood. There are several different patterns of inheritance observed in ACM: **1*) Autosomal dominant inheritance:*** In this pattern of inheritance, a person with a gene change predisposing them to ACM has a 50% chance of passing on that same predisposition to their child. We know that not everyone who inherits a gene change associated with ACM will develop ACM. This is called “reduced penetrance.” Among people in a family who get ACM there is variation in the severity of the disease and the age that ACM starts; ***2) Autosomal recessive inheritance:*** In this pattern of inheritance, an individual has to have two copies of a gene associated with ACM to get the disease. A person has a 25% chance

of inheriting both copies of the gene changes responsible for ACM (one from each parent). Each parent “carries” a gene changes but does not have ACM. This type of pattern is seen in Naxos island, a variant of ACM predominantly seen in Greece.[43] Autosomal dominant appears to be the most common pattern of inheritance; ***3) Compound heterozygosity and 4) Digenic mutations:*** Some families may experience more than one gene change, which may be classified as either compound heterozygosity or digenic mutations. In some families, the individual who carries the diagnosis of ACM may be found to have 2 different gene changes in the same gene (i.e. PKP2). This is called compound heterozygosity. Sometimes individuals with ACM can have gene changes in more than one gene (i.e. PKP2 and DSG2). This is referred to as ***4) Digenic inheritance*** (DI) it is the simplest form of inheritance for genetically complex diseases. By contrast with the thousands of reports that mutations in single genes cause human diseases, there are only dozens of human disease phenotypes with evidence for DI in some pedigrees.[44] In these situations, it is difficult to provide specific risk information to family members if they inherit only one of these gene changes because these same gene changes have also been observed alone in other individuals with ACM. Several laboratories worldwide, offer clinical genetic testing for many of the ACM-associated genes. The laboratories offering these services vary in price, number of genes screened, and technology used. Clinical genetic testing is available for the following ACM-associated genes. Mutations in these 6 genes account for ACM in 40-50% of patients screened: Plakophilin-2 (PKP-2) 12q11, 11% -43%, Desmoplakin (DSP) 6p24, Desmoglein-2 (DSG-2) 18q12, 1%-5%, Desmocollin-2 (DSC2), Plakoglobin (JUP) 17q21, and non-desmosome Transmembrane protein 43 (TMEM43).

The Johns Hopkins ACM Program, as well as the electrophysiology professional societies, strongly recommend that patients meet with a genetic counselor prior to any testing to discuss the benefits, risks, and limitations of genetic testing.

Genetic testing is recommended, and a pathogenic variant in an ACM-associated gene is considered a major criterion for diagnosis according to the 2010 TFC. The common genetic causes known to be associated with ACM are: DSC2, DSG2, DSP, JUP, PKP2, and TMEM43. Less common genetic causes include CTNNA3, DES, LMNA, PLN,[5] RYR2,[45] TGFB3,[46] TTN,[47, 48] CTNNA3.[4] A subset of these genes encode components of the desmosome.[38] Of 26 reported ACM:

1) Definitive causation genes (strong evidence): *PKP2*, *DSP*, *DSG2*, *DSC2*, *JUP*, and *TMEM43*;
2) Moderate evidence causation genes: *DES* and *PLN*;
3) Limited or no evidence (18 genes);
4) *RYR2* was refuted as an ACM gene since clinical data and model systems exhibited a CPVT. Table x

In ClinVar, only 5 pathogenic/likely pathogenic variants (1.1%) in limited evidence genes had been reported in ACM cases in contrast to 450 desmosome gene variants (97.4%).[49, 50]

Table 1 Causation and non-causation genes mutation following an international multidisciplinary ACM Clinical Genome Resource Gene Curation Expert Panel to reappraise all 26 reported ACM genes[50]

I Definitive causation genes (strong evidence)	II Moderate evidence causation genes	III Limited or no evidence	IV Refuted as an ACM gene
Desmosome (PKP-2, DSP, DSG-2, JUP	DES PLN	The remained 18 genes	RYR2
Non-desmosome (transmembrane protein 43 TMEM43)			

In contemporary ACM cohorts meeting 2010 Task Force Criteria (TFC), up to 65% of cases have P/LP pathogenic/likely pathogenic desmosomal variants.[4,5] 2015 professional guidelines[2] defined the term 'likely pathogenic' to mean with a 90% chance of pathogenicity. To determine whether current practice reflects this definition, ClinVar classifications were tracked from 2016 to 2019. During that period, between 83.8 and 99.1% of likely pathogenic classifications were reclassified as pathogenic, depending on whether LP to variant of unknown significance (VUS) reclassifications are included and on how these classifications are categorized.

ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 1; ARVD1, ACM/ARVC/D 1: Gene: The transforming growth factor beta (TGF-β) **/**TGF β 3; **Protein:** Transforming growth factor β-3 protein**.** Transmembrane protein 43; **Transforming growth factor, TFD β3; Chromosomal Cytogenetic location:** 14q23-q24/1**OMIM:** 107970; **Mendelian Inheritance** (MIM) 190230; **HGMD:** TGFB3 **Prevalence:** rare; **Inheritance pattern:** AD; **Clin Var:** TGFB3 **Author(s):** Beffagna et al.[46] *TGFβ3* modulates desmosomal expression,

desmosomal distribution and cell–cell stability. TGF-β superfamily is an important mediator of tissue repair. Each TGF-β isoform may exert a different effect on wound healing, which may be context-dependent. TGF-β1 may mediate fibrosis in adults' wounds, while TGF-β3 may promote scarless healing in the fetus and reduced scarring in adults. Thus, TGF-β3 may offer a scar-reducing therapy for acute and chronic wounds and fibrosing disorders.[51]

ARVC/D 2 Gene: *RYR2* (Ryanodine receptor-2 cardiac) **Currently it is refuted as an ACM gene variant; Chromosomal Cytogenetic location:** 1q42-q43**; Protein:** Ryanodine receptor 2;[45] **OMIM:** 600996**; HGMD:** RYR2; **Prevalence:** Rare: **Author(s):** Milting et al.[52] **Allelic disorders:** CPVT) an AD disorder, is characterized by stress-related, bidirectional VT in the absence of both SHD and a prolonged QT interval; CPVT may present with syncopal events in childhood and adolescence; mutation of RYR2 has been associated with early cardiac death.[53, 54] Altered calcium homeostasis may provide another pathogenic pathway in ARVC as suggested by pathogenic variants in *RYR2*. *RYR2* has an important role in calcium release from the sarcoplasmic reticulum and the regulation of excitation-contraction coupling. Impaired intracellular calcium content and altered excitation-contraction coupling may predispose to arrhythmias. In addition, impaired intracellular calcium may lead to cellular necrosis, promoting fibrosis and adipose replacement.[55] *RYR2* was refuted as an ACM gene since clinical data and model systems exhibited a CPVT phenotype.[50]

ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 3; ARVC/D 3; Gene:?; **Chromosomal Cytogenetic location:** 14q12-q22;[56] **OMIM:** 602086**; Prevalence: Unknown Inheritance:** AD; **Author(s):** Rampazzo et al. identified ARVC maps to chromosome 14q23-q24 in two families, one of which has 82 subjects (19 affected) in four generations. The pre-symptomatic identification of ARVD carriers by linkage analysis in the affected families strongly increases the possibility of prevention of life-threatening complications.[57] Severini et al described three unrelated families with ACM according to strict diagnostic criteria, 13 of 37 members were considered to be affected. Linkage was found in the region 14q12-q22 in all three families (cumulative two-point lod score is 3.26 for D14S252), with no recombination between the detected **cytogenetic location** and the disease gene. With multipoint linkage analysis, a maximal cumulative lod score of 4.7 was obtained in the region between loci D14S252 and D14S257. These data indicate that a novel gene causing familial ARVD (provisionally named ARVD2) maps to the long arm of chromosome 14, thus supporting the hypothesis of genetic heterogeneity in this disease.[56]

ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, ARVC/D 4 Gene: TTN (other names: CMPD4, CONNECTIN, EOMFC, LGMD2J TITIN_HUMAN, TMD). The *TTN* gene provides instructions for making a very large protein called titin;[58] **Protein:** titin. This protein plays an important role in muscles the body uses for movement (skeletal muscles) and in heart (cardiac) muscle. Slightly different versions (called isoforms) of titin are made in different muscles. Within muscle cells, titin is an essential component of sarcomeres; the basic units of muscle contraction; they are made of proteins that generate the

mechanical force needed for muscles to contract. Titin has several functions within sarcomeres: provide structure, flexibility, and stability to these cell structures. Additionally, interacts with other muscle proteins, including actin and myosin, to keep the components of sarcomeres in place as muscles contract and relax. Titin also contains a spring-like region that allows muscles to stretch. titin mutations can cause ACM, a finding that further expands the origin of the disease beyond desmosomal proteins. Structural impairment of the titin spring is a likely cause of ARVC and constitutes a novel mechanism underlying myocardial remodeling and SCD).[48] Finally, titin plays a role in chemical signaling and in assembling new sarcomeres;[59, 60] **Chromosomal Cytogenetic location:** 2q32.1-q32.3;[61] and 2q31, span ~0.3 Mb;[62-64] **OMIM:** 602087; **Inheritance:** AD; **Prevalence: Unknown; Author(s):** Rampazzo et al. in studies of 3 families, mapped a novel ARVD Chromosomal **cytogenetic location** to 2q32.1-q32.3, within the chromosomal region including markers D2S152, D2S103, and D2S389. Affected members of the 3 families showed clinical features typical of ARVD according to the diagnostic criteria of McKenna et al.[65] One family had been previously described by Kirsch et al.[66] Two instances of juvenile SCD had occurred and had been found at autopsy to be the result of ARVD. The families were considered unusual in the finding of localized involvement of the LV with LBBB in some affected members. **Other phenotypes:** Alagille syndrome (AGS - OMIM 118450), a multi-system, dominantly inherited developmental disorder). AGS maps to 20p12 and is mainly caused by haploinsufficiency of the Jagged-1 gene (*JAG1*- OMIM 601920), due to mutations in 70% of the cases and to deletions in 3-7% of the patients.[67] The clinical manifestations of the syndrome

are highly variable, ranging from slight clinical findings to major symptoms in 5 domains: cardiac, skeletal, ocular, facial and liver.

ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 5; ARVC/D5: is caused by heterozygous mutation in the TMEM43 gene (612048); **Gene:** TMEM43**; Protein:** Transmembrane protein 43; **Chromosomal Cytogenetic location:** mapped on chromosome 3p25.1.[68] 30-cM region on chromosome 3p22-p25 also contains a locus for ARVD5 and the cardiac sodium channel gene (SCN5A), mutations that cause familial isolated progressive cardiac conduction defect (Lenegre disease), lLQT3, and BrS;[69] **OMIM:** 604491; **Phenotypes associated: with** TMEM43 **mutations involucre both ventricles;**[70] **Prevalence:** Unknown; **Inheritance:** lethal AD cause of SCD in young people, prevalent in Newfoundland and Labrador;[71] **Phenotypes: Author(s):** Mener et al in 15 unrelated families from Newfoundland segregating ARVD mapping to chromosome 3p25,[70] performed bidirectional resequencing of 20 physical candidate ARVD5 genes and identified 1 rare variant, S358L in the TMEM43 gene (612048.0001), that was present in all 83 clinically affected individuals tested. The mutation was not found in 47 spouses or in 161 controls, and 35 (57%) of 61 'unaffected' individuals who carried the mutation were found to have clinical signs of ARVD on subsequent testing. Median age to develop an ARVD5-associated phenotype was 32 years for males and 44 years for females; penetrance was 100% in males and females by ages 63 and 76 years, respectively. Survival was significantly reduced in affected individuals, with a median survival of 41 and 71 years in affected males and females, respectively (relative risk is 6.8 times greater in affected males vs females).

Christensen et al[72] analyzed the TMEM43 gene in 55 Danish probands who fulfilled the criteria for ARVD and 10 patients with only some features of ARVD, and identified 1 woman with the S358L variant, which was also detected in her affected mother and not found in 650 ethnically matched controls. The proband, who fulfilled criteria for ACM, was negative for mutation in 6 known ACM-associated genes and did not show any large genomic rearrangements. Immunostaining of patient myocardium for TMEM43 and plakoglobin (173325) showed reduced signals for both compared to controls, suggesting that TMEM43-associated ACM shares a final common pathway with desmosome-associated ACM.

Baskin et al analyzed DNA samples from 195 unrelated individuals with suspected ACM for mutations in 4 ACM-associated desmosomal genes as well as the TMEM43 gene. Twenty-eight patients had disease-causing mutations in DSP (125647), PKP2 (602861), DSC2 (125645), or DSG2 (125671). Six patients carried the S358L 'Newfoundland' mutation in TMEM43, including a 43-year-old New Zealand man who was not of Newfoundland descent. In the New Zealand patient, the mutation arose de novo and on a haplotype distinct from that of the Newfoundland patients. In addition, 5 different rare missense variants in the TMEM43 gene were identified in 5 patients, 2 of whom also carried a variant in PKP2 and DSP, respectively.[6, 54, 73] The most important parameters to consider when determining arrhythmic risk include electric instability, including the frequency of PVCs and sustained ventricular arrhythmia; proband status; extent of structural disease; cardiac syncope; male sex; the presence of multiple mutations or a mutation in TMEM43; and the patient's willingness to restrict exercise and to eliminate participation in competitive or endurance exercise.[74, 75]

It is the most aggressive heterozygous form of ACM. It is predominantly caused by a fully penetrant mutation (p.S358L) in the non-desmosomal gene TMEM43-endemic to Newfoundland, Canada. To date, all familial cases reported worldwide share a common ancestral haplotype. It is unknown whether the p.S358L mutation by itself causes ARVC-5 or whether the disease is influenced by genetic or environmental factors. ARVC-5 is associated with a high risk of SCD and characteristic clinical and ECG features irrespective of geographical origin and genetic background. It is as in desmosomal ACM; TMEM43 (transmembrane protein 43)–S358L show fibrofatty replacement of the myocardium and die at a young age. This model confirms that TMEM43 is localized mostly at the nuclear membrane and provides new information on the pathophysiological mechanism of ARVC5. As in other forms of ARVC, the glycogen synthase kinase-3β signaling pathway plays an important role in this disease. Using this animal model, the authors tested 2 new therapeutic approaches for ARVC5, for which there are currently no effective therapies to prevent disease progression in humans. Although the antifibrotic drug GM-CT-01 did not show a beneficial effect on transgenic mice expressing TMEM43-S358L, inhibition of glycogen synthase kinase-3β improved cardiac function and survival, opening the way to a new therapeutic approach focused on glycogen synthase kinase-3β inhibition that could be used in humans with ARVC5 in the future.[76]

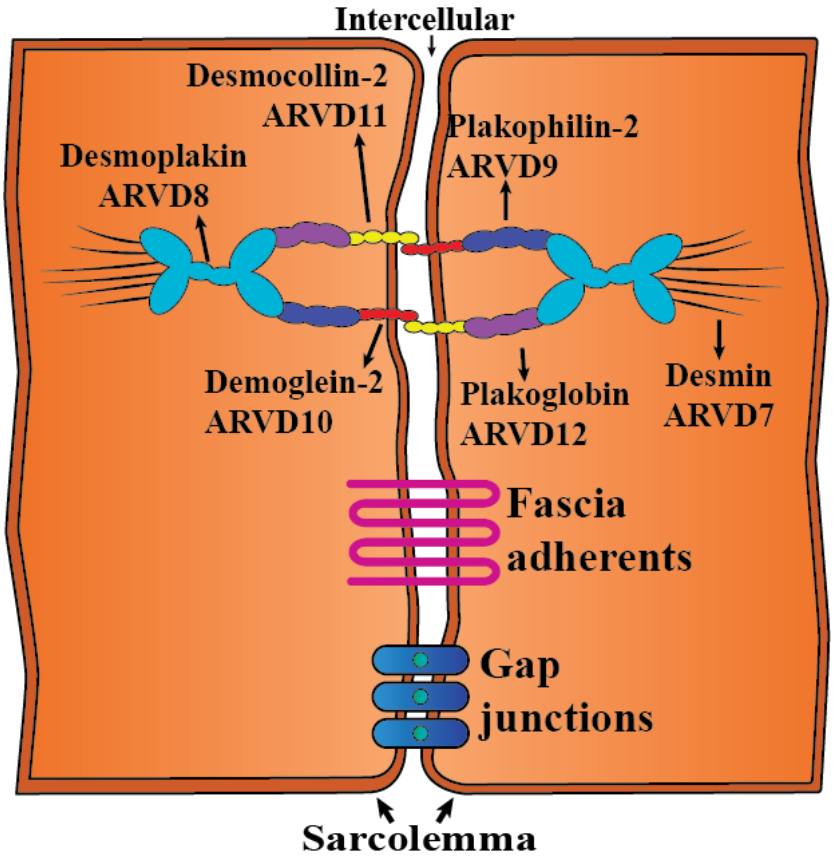
ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 6;

ARVC/D 6 Gene symbol: DES/ DESM_HUMAN; **Gene Nomenclature Committee:** 2770; **Protein:** Desmin; both the head and tail of desmin have been identified as causative of ACM.[77] Also association with Desmin-related myopathy

(van Tintelen).[78]Skeletal myopathy, **severe generalized myopathy,[79]** DCM (%++ of DCM caused by pathogenic variants in this gene: <1%. MOI: AD, Distinguishing clinical features: Arrhythmia & neuromuscular involvement, Allelic Disorders 3: Desminopathy Myofibrillar myopathy, OMIM: 125660, PS601419. arrhythmia uncommon as an early feature; **Chromosomal Cytogenetic location:** mapped on chromosome *10p14-p12;*, **OMIM:** 604401; Klauke et al [2010], Otten et al [2010], Hedberg et al [2012], Lorenzon et al [2013]; **Phenotypes associated:** DES mutations involucre both ventricles;[80] **Cellular complex:** Intermediate filament; **Prevalence:** Unknown; **Inheritance Pattern:** AD; **Prevalence:** Unknown; **Author(s):** Li et al[81, 82]; **Phenotype MIM number:** 604401.

A dysfunctional desmin mutation in a patient with severe generalized myopathy.

Figure



A schematic diagram of the desmosome. Desmoglein (ARVD 10) and desmocolin (ARVD 11) located in the transmembrane region connect with the corresponding molecules on the neighboring cell and are linked to desmoplakin (ARVD 8) by plakophilin (ARVD 9) and plakoglobin (ARVD 12). Desmin (ARVD 7).

ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 7;

ARVC/D 7 Gene: DES or DESM_HUMAN**; Chromosomal Cytogenetic location:** mapped to chromosome 10q22. which was later found to be a form of myofibrillar myopathy (MFM1; 601419) caused by mutation in the DES gene (125660) on chromosome 2q35.; **OMIM:** 609040. **Prevalence:** 2-3%; Note: Bermudez-Jimenez et al reported the largest known family carrying a single *DES* mutation (DES-p.Glu401Asp), which predominantly causes inherited ACM, suggested that the prevalence of *DES* mutations in ACM is higher.[77]

Several reports described patients who fulfil the so-called ARVC 2010 Task Force Criteria and are carriers of *DES* mutations.[9, 80, 83-85]

The DES gene: This gene encodes a muscle-specific class III intermediate filament. Homopolymers of this protein form a stable intracytoplasmic filamentous network connecting myofibrils to each other and to the plasma membrane. Mutations in this gene are associated with desmin-related myopathy, a familial cardiac and skeletal myopathy (CSM), and with distal myopathies provides instructions for making a protein called desmin. Desmin is found in cardiac muscle and skeletal muscle. Within muscle fibers, desmin proteins are important to help maintain the structure of sarcomeres, which are necessary for muscles to contract. Desmin proteins surround rod-like structures called Z-discs of the sarcomere, connecting them to one another, linking neighboring sarcomeres and forming myofibrils, the basic unit of muscle fibers. The connection of sarcomeres to each other to form myofibrils is essential for maintaining muscle fiber strength during repeated cycles of contraction and relaxation; **Phenotypes associated:** with DES mutations involucre both ventricles:[80]

1) Myopathy mifibrillar MFM1 or desmin-related myopathy(DRM) (Skeletal myopathy).[86], Phenotype MIM number: 601419,Inheritancepattern AD/AR
2) Dilated Cardiomyopathy (DCM).
3) ARVC-like phenotype arrhythmia uncommon as an early feature.
4) *Neurogenic Scapuloperoneal Syndrome, Kaeser Type.*[87]

Otten et al confirmed that either an ARVC-like phenotype or a severe cardiomyopathy with RV involvement are possible, yet infrequent, cardiac phenotypes in DRM. Moreover, the authors demonstrated that the DES mutation p.R454W affects the localization of desmoplakin and plakophilin-2 at the

intercalated disk, suggesting a link between desmosomal cardiomyopathies (mainly affecting the RV) and cardiomyopathies caused by DES mutations.[78] Only a missense mutation in the DES gene coding for desmin, the intermediate filament protein expressed by cardiac and skeletal muscle cells, has been associated with ACM. Data from Lorenzon et al postulate that in the absence of skeletal muscle (desminopathy), the probability of DES mutations in ACM is very low.[9, 78, 88, 89]

ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 8;

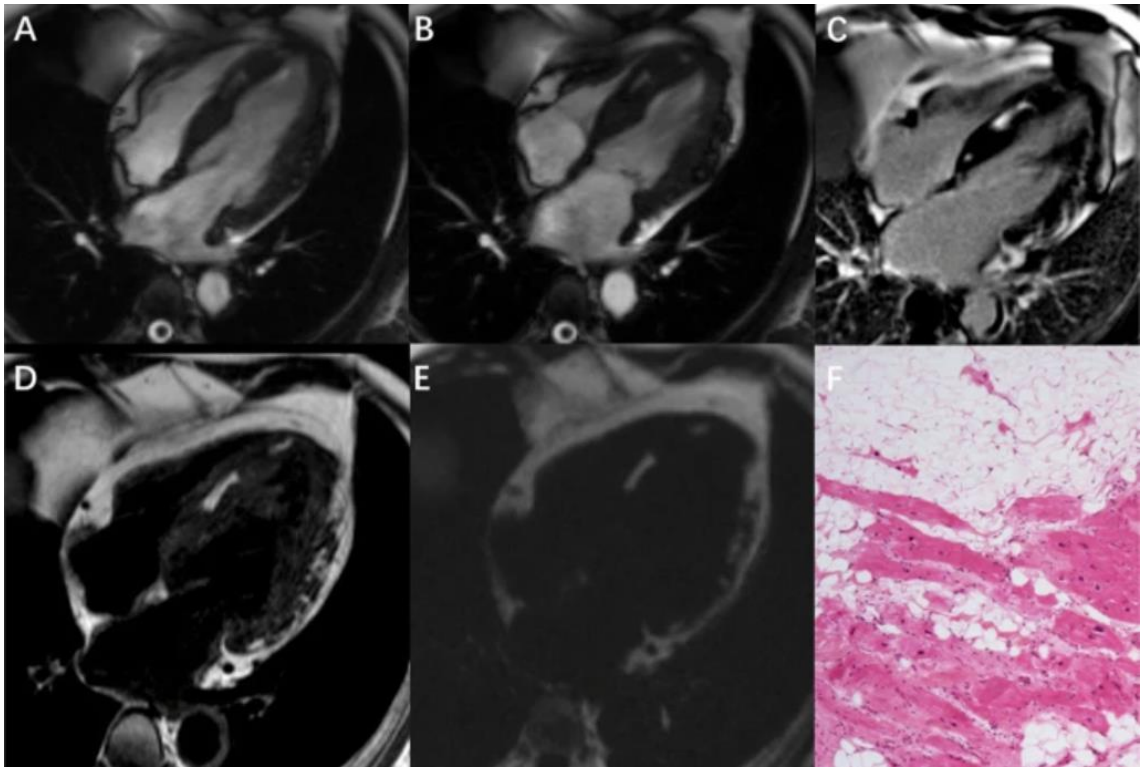
ARVC/D 8 Gene: is caused by heterozygous mutation in the gene DSP that encoding desmoplakin (DSP; 125647) on chromosome 6p24. Mutations in DSP gene have strong evidence of being a cause of ACM.; **Protein:** Desmoplakin;[90] **Structure:** Desmosome; **Chromosomal Cytogenetic location:** mapped to chromosome 6p24.3**; OMIM:** 607450**; Phenotypes associated:** predominant LV disease, biventricular predominant and cardio cutaneous syndrome;[91] **Gene Nomenclature Committee (HUGO):** 3052; **Prevalence: ?; Author(s):** Rampazzo et al,[91] Yang et al,[92] Christensen et al.[93]

Truncating mutations in *DSP* or digenic/compound heterozygosity of desmosomal genes are associated with more aggressive phenotypes and can be considered as risk factors of SCD and CHF.[38] **Genotype-Phenotype correlations**: *DSP* variants are more likely to be associated with left ventricular dysfunction.[38, 94] Carvajal syndrome, characterized by ventricular dilated cardiomyopathy, palmoplantar keratoderma, and woolly hair is associated with *DSP* homozygous pathogenic variants.[94-98] For ACM patients, both missense and non-missense DSP mutations carry a high arrhythmic risk. Non-missense

mutations are specifically associated with left-dominant forms (LDAC). New diagnostic criteria for the diagnosis of ACM include TWI in V4–V6 as a marker of LV involvement. Additionally, TWI in inferior leads may be sensitive markers of ALVC even in the absence of ventricular remodeling. LV dysfunction and LV structural involvement are significantly more common in carriers of non-missense mutations.[99-101]

López-Ayala et al identified a new desmoplakin mutation (DSP c.1339C.T) associated with a severe phenotype of ACM and a high burden of ventricular arrhythmia. LV non-compaction with high personal and familiar arrhythmic burden should arouse suspicion towards desmosomal disease. Vast majority of desmoplakin truncated mutations reported in the literature are associated with severe phenotypes.[94]

The presence of DSP non-missense mutations should alert to the likely development of LV-CHF. These findings highlight the clinical relevance of genetic testing even after the clinical diagnosis of ACM and the growing clinical impact of genetics.[102] Abnormal myocardial stretch, dilatation later fibrosis and progressive cardiac failure. Common features are: non compacted LV and recurrent VT/VF with SCD. Predominant LV involvement. Fatty infiltration is less common. Figure x



A typical case of ACM in a 54-year-old male patient with frequent PVCs and syncope. Four chamber view of (**A**) End-diastolic Steady-State Free Precession (SSFP) cine, (**B**) End-systolic SSFP cine, (**C**) LGE (**D**) T1 weighted image and (**E**) fat image from water-fat separation imaging all show fibro-fatty infiltration in the interventricular septum and the epicardial LV lateral wall. The contour of the lateral LV wall is irregular with a “serrated” shape. LGE shows significantly delayed enhancement of the LV basal to mid lateral wall, interventricular septum and adjacent anterior wall. (**F**) EMB showing areas of fibro-fatty infiltration and replacement of the myocardium.

ARVC/D 9 (OMIM Entry); Gene: PKP2. Mutations in this gene have strong evidence of being a cause of ACM.**; Protein:** Plakophillin-2; **Structure:** Desmosome; **Type of mutation:** Non-missense++(splice-site, nonsense, ins/del, large del), Missense **Chromosomal Cytogenetic location:** mapped to chromosome 12p11.21**; OMIM:** 609040**; Phenotypes associated:** predominant

RV disease, and biventricular predominant;[38, 103] **Mode of inheritance:** AD+++/AR 25–40%;[103] **Phenotype AR/ Compound Heterozygous:** ARVC† DCM†; **Reported incidence:** 20%–45%; **Prevalence:** 40%-10%.[41] *PKP2* represents the most common gene mutated in ACM, with a prevalence ranging from 40% (identified as the sole cause of ACM in the cohort) to approximately 10%;[104] **Genotype-Phenotype Correlations:** *PKP2* pathogenic variants are more likely to be associated with VT.[105]

Penetrance of *PKP2* mutations was higher with increased age and male sex, with male mutation carriers more likely than female mutation carriers to have both structural and conduction abnormalities.[106]

The first human desmosomal mutations were reported in PKP1 (plakophilin 1) in 1997;[107] the clinical abnormalities affected skin, hair and nails and were described as “ectodermal dysplasia-skin fragility syndrome” Subsequently, monoallelic and biallelic mutations have been reported in several further genes encoding transmembranous and plaque proteins of desmosomes that give rise to a spectrum of genodermatoses affecting the skin, hair, mucous membranes and extracutaneous sites, notably the heart New desmosomal genodermatoses reported, include new diseases associated with mutations in DSG1, DSP and DSC3 as well as new gene additions such as PERP and DSG3.[108]

Author(s): Grossmann et al[109] hypothesized that mutations in human PKP2 may account for ACM. They collected samples from a total of 120 unrelated ACM probands of Western European descent (101 males and 19 females) who were diagnosed using criteria proposed by McKenna et al. (1994). Gerull et al sequenced all 14 PKP exons, including flanking intronic splice sequences, and

identified 25 different heterozygous mutations in 32 probands (27 males and 5 females) (see, e.g., 602861.0001-602861.0004).[103]

Mutation carriers, especially PKP2, had a higher proportion of a history of VT and more inducible rapid VT.[105]

Klauke et al in a cohort of 22 patients with ACM referred to molecular genetic screening screened for desmin mutations found a novel desmin-mutation p.N116S in a patient with ACM and terminal CHF, which is located in segment 1A of the desmin rod domain. The mutation leads to the aggresome formation in cardiac and skeletal muscle without signs of an overt clinical myopathy. Cardiac aggresomes appear to be prominent, especially in the RV. Viscosimetry and atomic force microscopy of the desmin wild-type and N116S mutant isolated from recombinant Escherichia coli revealed severe impairment of the filament formation, which was supported by transfections in SW13 cells. The gene coding for desmin appears to be a novel ACM gene, which should be included in molecular genetic screening of ACM patients.[9]

Very rarely PKP2 The first iPSC-based model carrying a relatively infrequent mutation in PKP2 (c. 2484C>T) was identified by Cerrone et al. This mutation causes BrS symptoms and a reduced INa, deficit that can be restored in vitro at the cellular level via transfection of wild-type PKP2.[110] Penetrance of *PKP2* mutations was higher with increased age and male sex, with male mutation carriers more likely.

Kapplinger et al were the first to perform a comprehensively evaluate genetic variation in healthy controls for the ACM susceptibility genes. They concluded that radical mutations are high-probability ACM-associated mutations, whereas

rare missense mutations should be interpreted in the context of race and ethnicity, mutation location, and sequence conservation.[93, 104, 111-113]

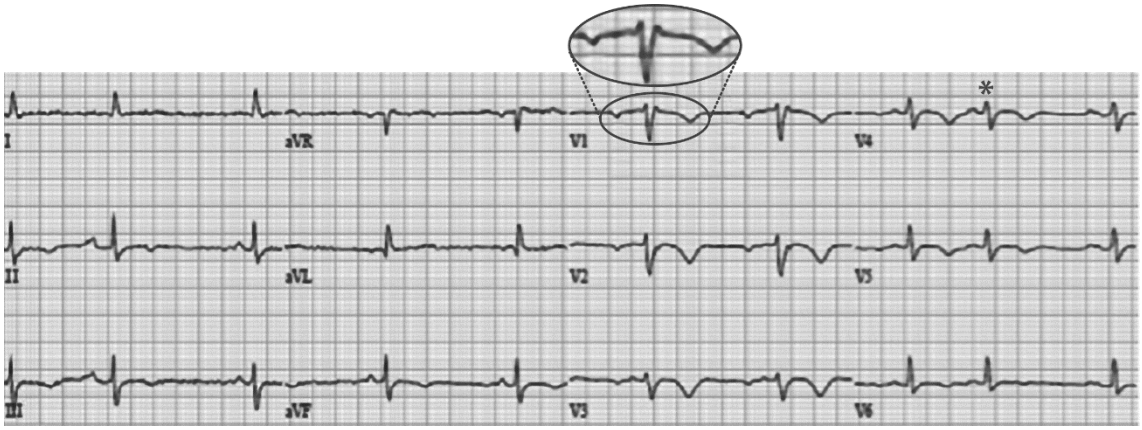


Figure. 12- lead ECG shows sinus bradycardia (HR 48 bpm), parasinusal premature contraction (*), prolonged PR interval (275 ms), TWI across the precordial leads (V1-V6) and inferior leads, epsilon waves insinuation.

Multiple inducible VTs were present of LBBB pattern with inferior and superior QRS axis (VT1-5).

ARVC with PKP2 mutations account for the vast majority of ACM, leading to the classical RV dominant ACM phenotype.

ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL,10;

Gene: DSG2 **ARVC/D (OMIM Entry); 10;** Mutations in DSG2 gene have strong evidence of being a cause of ACM. Award et al reported that mutations in *DSG2* contribute to the development of a ACM in the absence of mutations in *PKP2* or *DSP.* This provides further evidence that disruption of the cardiac desmosome is important in the pathogenesis of this condition. Since SCD is a prominent manifestation of ACM, recognition of those at highest risk of developing the condition may be improved by genetic screening within affected families.[114] This gene encodes a member of the desmoglein family and cadherin

cell adhesion molecule superfamily of proteins. Desmogleins are calcium-binding transmembrane glycoprotein components of desmosomes, cell-cell junctions between epithelial, myocardial, and other cell types. The encoded preproprotein is proteolytically processed to generate the mature glycoprotein. This gene is present in a gene cluster with other desmoglein gene family members on chromosome 18. Mutations in this gene have been associated with arrhythmogenic right ventricular dysplasia, familial, 10; **Protein:** Desmoglein-2; **Structure:** Desmosome; **Type of mutation:** Non-missense (splice-site, nonsense, ins/ del) Missense; **Chromosomal Cytogenetic location:** mapped to chromosome 18q12.1-q12; **OMIM:** * 125671**; Phenotypes associated:** predominant RV disease, biventricular and predominant LV disease.[38, 41] **Mode of inheritance:** AD+++, AR. Genetic analyses performed by Brodehl et al of two independent ACM index patients without obvious familial anamnesis revealed homo- or hemizygous LoF mutations in *DSG2*. Therefore, the authors suggest also for ACM patients without further affected family members a genetic counseling and analysis, because putative pathogenic mutations might be hidden by a recessive inheritance.[115] **Phenotype AD:** ARVC BiVCM; **Frequency in ACM:** 4%–15%; **Phenotypes:** Arrhythmogenic Right Ventricular Dysplasia, Familial, 10 (Phenotype MIM number 610193) and Dilated Cardiomyopathy, Dilated, 1Bb (Phenotype MIM number 612877)**.** Among its related pathways are keratinization and ARVC. Gene Ontology (GO) annotations related to this gene include calcium ion binding and cell adhesive protein binding involved in bundle of His Cell-Purkinje myocyte communication. An important paralog of this gene is DSG4. **Reported Incidence:** 12%-40% 1%-5%; **Author(s):** Pilichou et al,[41] Awad et al,[114] Brodehl et al.[115]

Anti-DSG2 antibodies are a sensitive and specific biomarker for ACM. The development of autoimmunity as a result of target-related mutations is unique. Anti-DSG2 antibodies likely explain the cardiac inflammation that is frequently identified in ACM. and may represent a new therapeutic target.[116]

The desmosome is a type of intercellular junction found in epithelial cells, cardiomyocytes and other specialized cell types. Mutations in DSG2 gene can result in cardio cutaneous syndromes together wit, JUP and, DSP. although mutations have been described in five genes in inherited heart disorders that may lack any dermatological manifestations (DSG2, DSC2.[117]

Main references on Desmoglein-2 Awad et al. 2006a Pilichou et al. 2006; Syrris et al. 2007; Posch et al. 2008; Yu et al. 2008; Bhuiyan et al. 2009; den Haan et al. 2009; Christensen Fressart et al. 2010et al. 2010a Cox et al. 2010; Gehmlich et al. 2010 Xu et al. 2010; Lahtinen et al. 2011; Nakajima et al. 2011 Gehmlich et al. 2011b; Kapplinger et al. 2011; Sato et al. 2011.

ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 11;

ARVC/D 11: (OMIM Entry); # 610476**.; Gene:** DSC2. Mutations in DSC2 gene have strong evidence of being a cause of ACM.; **Protein:** Desmocollin-2(DSC 2)**; Structure:** Desmosome**.; 611528; Chromosomal Cytogenetic location:** mapped to chromosome 18q12.1; **OMIM:** 610476; **Phenotypes associated:** predominant RV disease, and biventricular:[5, 117] **a) Gene Locus MIM number:** 125645. **(AD)** and b) ARVD 11 with mild palmoplantar keratoderma and woolly hair: AR.[117] **Inheritance:** AD/AR. Two sibs, offspring of consanguineous parents, had ACM, mild palmoplantar keratoderma, and woolly hair; the sibs were homozygous for a base pair deletion. **Reported incidence:** 2-7%; **Author(s)**:

Greenwood et al,[118] Brodehl et al.[119] Greenwood et al. found that the human DSC2 gene, contains 17 exons ranging in size from 46 to 258 bp and spans more than 32 kb of DNA. Exon 16 is alternatively spliced, giving rise to the a and b forms of the protein. A remarkable degree of conservation of intron position with other cadherins was observed.[118] Heuser et al investigated 88 unrelated patients with ACM for mutations in DSC2 gene. They identified a heterozygous splice acceptor site mutation in intron 5 of the DSC2 gene, which led to the use of a cryptic splice acceptor site and the creation of a downstream premature termination codon. Quantitative analysis of cardiac DSC2 expression in patient specimens revealed a marked reduction in the abundance of the mutant transcript. Morpholino knockdown in zebrafish embryos revealed a requirement for DSC2 in the establishment of the normal myocardial structure and function, with reduced desmosomal plaque area, loss of the desmosome extracellular electron-dense midlines, and associated myocardial contractility defects. These data identified DSC2 mutations as a cause of ACM in humans and demonstrated that physiologic levels of DSC2 are crucial for normal cardiac desmosome formation, early cardiac morphogenesis, and cardiac function.[99, 120] De Bortoli et al. detected the 2-bp insertion (125645.0002), which they designated A897KfsX4, in 5 unrelated Italian ARVD probands, 4 of whom were known to carry mutations in other ARVD genes as well. The A897KfsX4 variant was also found in 6 of 400 control chromosomes (allele frequency, 1.5%). Noting that the A897KfsX4 variation affects only the DSC2a isoform and not DSC2b, which shows higher expression in the heart than does DSC2a, the authors suggested that relative deficiency of DSC2a might be compensated for by DSC2b and that A897KfsX4 should be considered a rare polymorphism.[121] In 6 affected individuals from 2

Canadian Hutterite kindreds with ARVD, Gerull et al. identified homozygosity for a c.1660C-T transition in the DSC2 gene, resulting in a gln554-to-ter (Q554X) substitution within the fourth extracellular cadherin domain. The mutation segregated fully with disease in the 2 families; it was also found at a carrier frequency of 9.4% in a sample of 1,535 Schmiedeleut Hutterites from South Dakota, among whom 6 homozygotes were detected. Immunohistochemistry of endomyocardial biopsy samples from homozygous individuals showed altered expression of the truncated DSC2 protein at the intercalated discs, but only minor changes in immunoreactivity of other desmosomal proteins. Recombinant-expressed mutant DSC2 in HEK293 and HeLa cells confirmed a stable, partially processed truncated protein with cytoplasmic and membrane localization. Mild palmoplantar hyperkeratosis was observed in only 1 of the Canadian Hutterite patients, who had normal hair.[122] They suggested that involvement of hair and skin, as observed in a family of Pakistani origin by Simpson et al, might be dependent on the exact location of the mutation or a modifying genetic/ethnic background.[123]

Main references on Desmocollin-2: Heuser et al. 2006; Syrris et al. 2006b. Beffagna et al. 2007; Simpson et al;[5] Christensen et al. 2010a. Cox et al. 2010, de Bortoli et al. 2010. Xu et al. 2010

ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 12; ARVC/D 12: OMIM Entry): * 173325 **Gene:** JUNCTION PLAKOGLOBIN (JUP) (Rare);[43, 123] This genetic mutation is among the common genetic causes associated with ACM: DSC2, DSG2, DSP, **JUP**, PKP2, and TMEM43.[124] Applying the Clinical Genome Resource approach to gene-disease

curation, only *PKP2*, *DSP*, *DSG2*, *DSC2*, ***JUP*****,** *TMEM43*, *PLN*, and *DES* genes had definitive or moderate evidence for ACM, and these genes accounted for nearly all pathogenic/likely pathogenic ACM variants in ClinVar. (ClinVar is a freely accessible, public archive of reports of the relationships among human variations and phenotypes, with supporting evidence. ClinVar is a freely accessible, public archive of reports of the relationships among human variations and phenotypes, with supporting evidence.). Consequently, only pathogenic/likely pathogenic variants in these genes should yield a major criterion for ACM diagnosis;[50] **Protein:** Plakoglobin (JUP); Junction.; **Structure:** Plakoglobin (JUP) desmosome protein; **Chromosomal *Cytogenetic location:*** mapped to chromosome 17q21.2; **OMIM:** 611528**; Phenotypes associated:** predominant RV disease, biventricular and cardio cutaneous syndrome;[125] **Phenotype MIM number:** 173325; HGNC ID(HUGO Gene Nomenclature Committee: 6207;b **Reported incidence:** Rare; **Mode of inheritance:** AR: Naxos disease (ACM) with palmoplantar keratoderma and peculiar woolly hair) is caused by homozygous pathogenic variants;[125] Additionally, penetrance is complete by adolescence.[126]

Naxos disease.[43] JUP @ Leiden Open-source Variation Database (LOVD) Gene Connection for the Heart LOVD Website (http://www.LOVD.nl/); Naxos disease database (JUP) ARVD/C Genetic Variants Database – JUP. Asimaki et al. described a German family in which the father and 3 sons had ACM. The proband experienced syncope at age of 39 years. After a documented episode of sustained VT, he was admitted to the hospital for further diagnostic evaluation and management. ECG demonstrated wide QRS, TWI, and LPs from V1 to V3. Angiography showed moderate global RV dilatation and regional wall-motion

abnormalities without LV involvement. Sustained MVT of LBBB pattern was induced at EPS. EMB showed extensive fibrofatty replacement of RV muscle and patchy mononuclear inflammatory infiltrate. These phenotypes led to the diagnosis of ACM. Skin and hair appeared grossly normal. The proband's brothers received diagnoses of ACM after cardiac evaluation on the basis of ECG, Holter and TTE abnormalities.[123]

Other non-desmosome causative genes

Nuclear envelope proteins/ **Gene**: LMNA; ***Cytogenetic location*****:** mapped to chromosome 1q22: **MIM:** 150330; **Protein:** Lamin A/C; HGNC ID (HUGO) **Gene Nomenclature Committee:** 6636; **Inheritance:** AD. Lamins are type V filaments that serve a variety of roles, including nuclear structure support, DNA repair, cell signaling pathway mediation, and chromatin organization. A major gene associated with DCM with cardiac conduction system disease is lamin A/C (LMNA) gene. In 1999, LMNA was found responsible for Emery-Dreifuss muscular dystrophy and, since then, has been found in association with a wide spectrum of diseases termed laminopathies, including LMNA cardiomyopathy. Patients with LMNA mutations have a poor prognosis and a higher risk for SCD, along with other cardiac effects like dysrhythmias, development of CHF, and potential need of a pacemaker or ICD implantation. As of now, there is no specific treatment for laminopathies, including LMNA cardiomyopathy, because the mechanism of LMNA mutations in humans is still unclear. Lamin A/C gene mutations can be found in severe forms of ACM. Lamin A/C gene should be added to desmosomal genes when genetically testing patients with suspected

ACM, particularly when they also have ECG evidence for conduction disease.[127, 128]

Gene: ACTC1(nondesmosomal gene); **Protein:** Actin α cardiac muscle 1**; Cellular Complex:** Sarcomere: Sarcomeric variant;[129] **HGNC ID (HUGO):** 143

Note: Variants in the sarcomere genes identified upon sequencing of 137 probands with ACM were MYH7, MYBPC3, MYL3. All were considered with ACMG pathogenicity classification as VUS.[2]

Table x Desmosomal and non-desmosomal proteins main characteristics

Involved structure	Gene, Cytogenetic location, MIM, Protein, Inheritance	Reported incidence
Desmosomal proteins		
	ARVC9; **Gene:** PKP2; **Cytogenetic location:** mapped to chromosome 2p11: **MIM:** 609040; **Protein:** Plakophillin-2; **Frequency:** 20%–45%; **heritance:** AD/AR**.**	25–40 %
	Gene: DSC2; **Cytogenetic location:** mapped to chromosome 18q21; **MIM:** 125645; **Protein:** Desmocollin2; **Inheritance pattern:** AD	2–7 %
	Gene: DSG2; Cytogenetic location: mapped to chromosome 18q12.1;	5–10 %

	MIM:125671; **Protein:** Desmoglein-2; **Inheritance pattern:** AD/AR**.**	
	Gene: Desmoplakin PKP2; **Cytogenetic location:** mapped to chromosome **MIM:**; **Protein:**; **Inheritance pattern:.**	2–12 %
	Gene: Plakoglobin	Unknown
Non-desmosomal proteins		
Cytoplasmic molecules	α-T-catenin	Unknown
Calcium/sodium channels	Ryanodine receptor 2 or the cardiac ryanodine receptor (hRYR2).[45] Mutations in hRYR2 are typically associated with effort-induced polymorphic VT and juvenile SCD, without resting ECG abnormalities or structural abnormalities, and mutations in this gene are no longer classified as a subtype of ACM.	Unknown
	Gene: PLN; **Cytogenetic location:** mapped to chromosome 6q22.1: **MIM:** 172405; **Protein:** Phospholabam; **Inheritance pattern:** AD	Unknown
Nuclear envelope proteins/	**Gene**: LMNA; **Cytogenetic location:** mapped to chromosome 1q22: **MIM:**	Unknown

	150330; **Protein:** Lamin A/C; **Inheritance pattern:** AD	
Transmembrane proteins	**Gene**: TMEM43; **Cytogenetic location:** mapped to chromosome 3p31.2: **MIM:** 612048; **Protein:** Transmembrane protein 43; **Inheritance pattern:** AD	
Cytoskeletal proteins	**Gene:** DES/ DESM_HUMAN Klauke et al [2010], Otten et al [2010], Hedberg et al [2012], Lorenzon et al [2013]; **Cytogenetic location:** mapped to chromosome 2q35: MIM: 125660; **Protein:** Desmin; **Gene Nomenclature Committee: 2770**; **Inheritance pattern:** AD. Desmin. Pe both the head and tail of desmin have been identified as causative of ACM.[77] Also association with Desmin-related myopathy (van Tintelen).[78]Skeletal myopathy, DCM; arrhythmia uncommon as an early feature **Cytogenetic location:** mapped to chromosome 2q35, MIM: 607667; **Inheritance pattern:** AD	Unknown

Table 1. Genetic mutations associated with ACM.[38, 130, 131]

Genes associated with ACM (Source: http://www.cardiomyopathy.org).

Diagnosis/testing: The diagnosis of ACM is made using a combination of noninvasive and invasive tests to evaluate cardiac structure and rhythm. The common genetic causes known to be associated with ACM are: DSC2,[120] DSG2,[132] DSP,[133] JUP,[134] PKP2,[135] and TMEM43.[136] Less common genetic causes include CTNNA3,[4, 124] DES,[78] LMNA,[137] PLN,[138] RYR2 (currently refuted),[45] TGFB3,[46] and TTN.[47, 48] A subset of these 13 genes encode components of the desmosome.

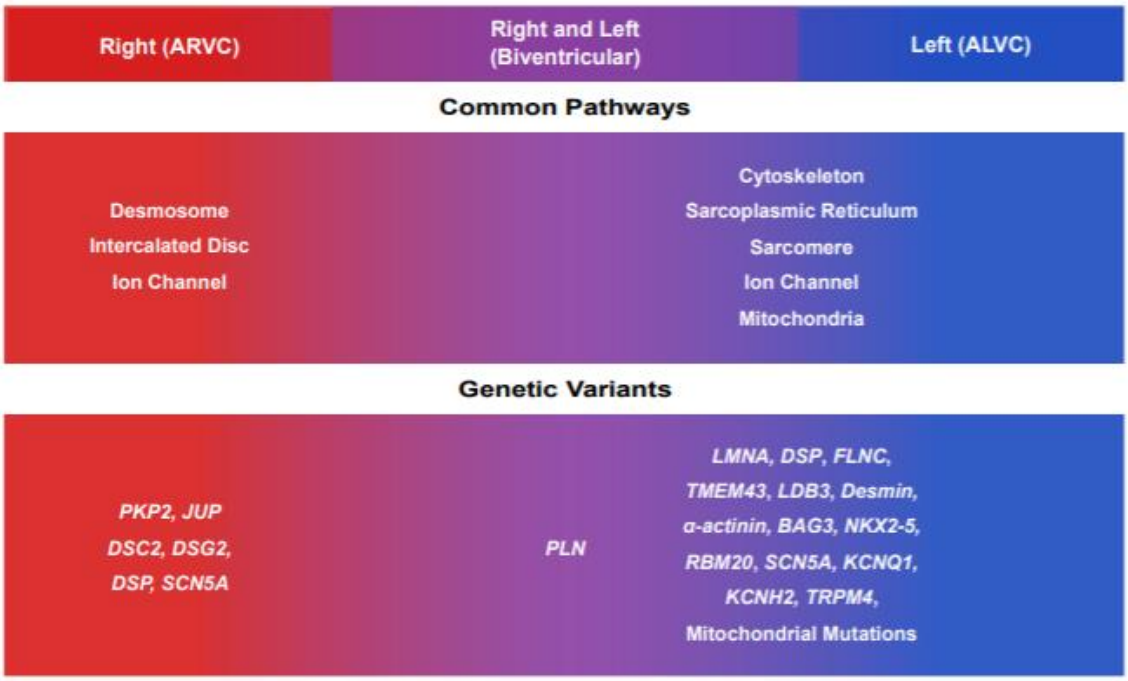
Arrhythmogenic Right Ventricular Cardiomyopathy: Genes and Databases.[43]

The diagnosis of ACM

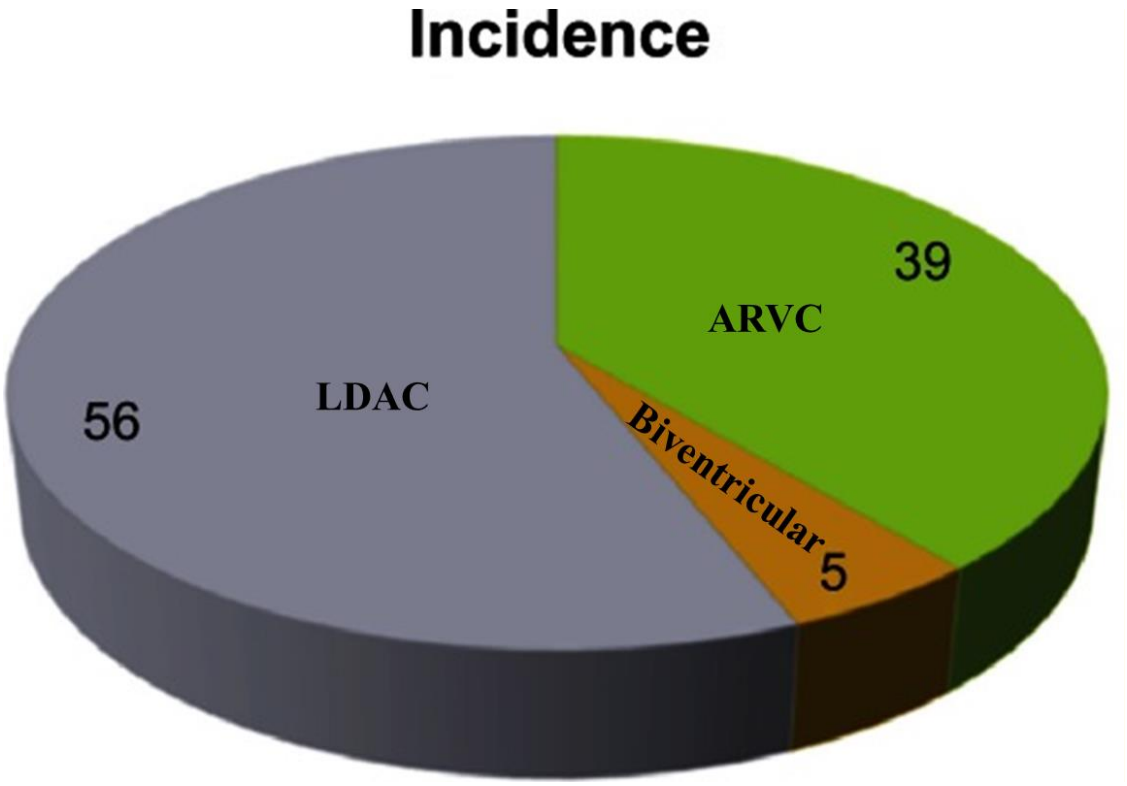
Diagnosis is based on the finding of a combination of multi-parametric approach encompassing characteristic abnormalities in family history /genetic background (Given that approximately half of genetic variants were reclassified, with 10.1% of patients losing their definite disease status, accurate determination of variant pathogenicity is of utmost importance in the diagnosis.), medical history, physical exam, 12-leads ECG, TTE, Holter monitor, CMRI, and/or cardiac CT scan, an EP study (spontaneous induced during EPS), angiography as well as EMB electro-anatomic voltage mapping (EMB)

Currently clinical variants

Right Arrhythmogenic Ventricular tachycardia, Left-dominant arrhythmogenic cardiomyopathy (LDAC)[139-143] or Right and Left (Biventricular),[84] and Arrhythmogenic LV cardiomyopathy (ALVC).[144]



Incidences of ventricular involvement in ACM. Classic form is mostly RV involvement, LV or Biventricular involvement.[145]



“The Padua criteria” for the diagnosis of Arrhythmogenic Cardiomyopathy 2020.[146]

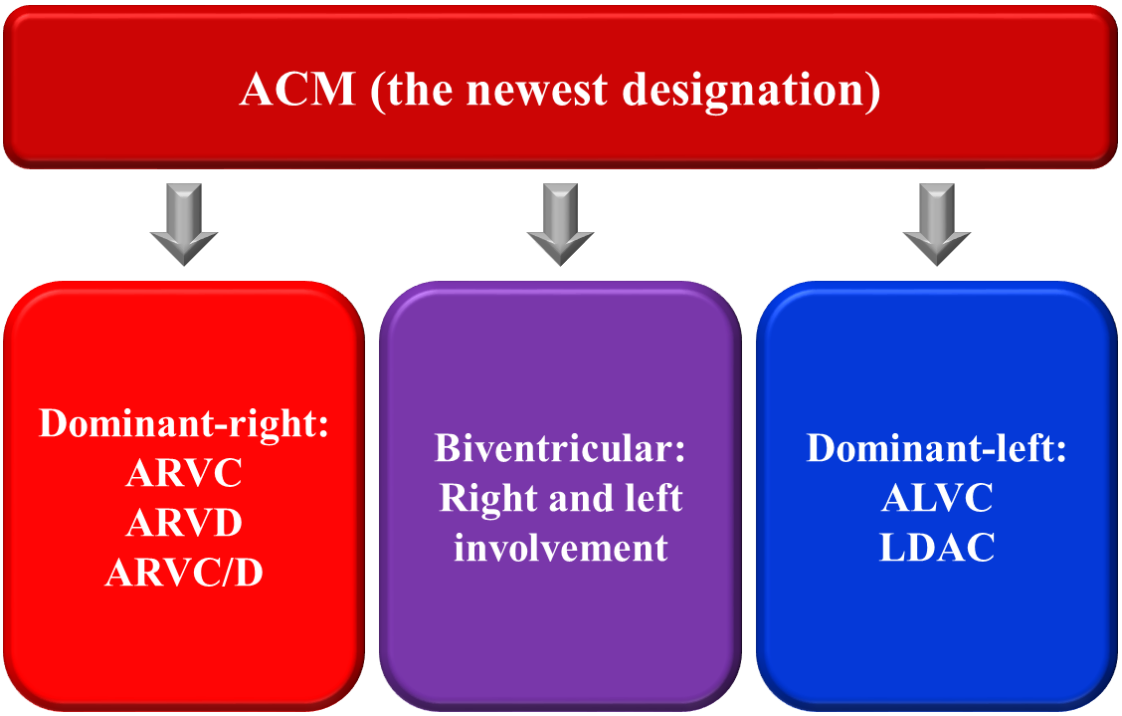


Figure. Left-dominant is a subtype characterized by early predominance of LV involvement. ACM: arrhythmogenic cardiomyopathy; ARVC: arrhythmogenic right ventricular cardiomyopathy; ARVD: arrhythmogenic right ventricular dysplasia; ARVC/D: arrhythmogenic right ventricular cardiomyopathy/dysplasia; ALVC: arrhythmogenic left ventricular cardiomyopathy; LDAC: left-dominant arrhythmogenic cardiomyopathy.

A. The classic form of ARVC, Dominant-Right, arrhythmogenic right ventricular dysplasia (ARVD); ARVC/dysplasia (ARVC/D) (ARVC). RV (Upgrade 2010 Task Force Diagnostic Criteria)

I. **Common Pathways:** Desmosome intercalated disk**/** Ion Channel

II. **Genetic Variants:** PKP2, JUP, DSC2, DSG2, DSP, SCN5A

III. **Morph-functional ventricular abnormalities:**

By echocardiography, CMRI or angiography:

Major: Regional RV akinesia, dyskinesia, or bulging plus one of the following:

- Global RV dilatation (increase of RV EDV according to the imaging test specific monograms for age and gender).
- Global RV systolic dysfunction (reduction of RVEF according to the imaging test specific monograms for age, sex, and BSA).

Minor: Regional RV akinesia, dyskinesia or aneurysm of RVFW.

IV. ***Structural myocardial abnormalities***

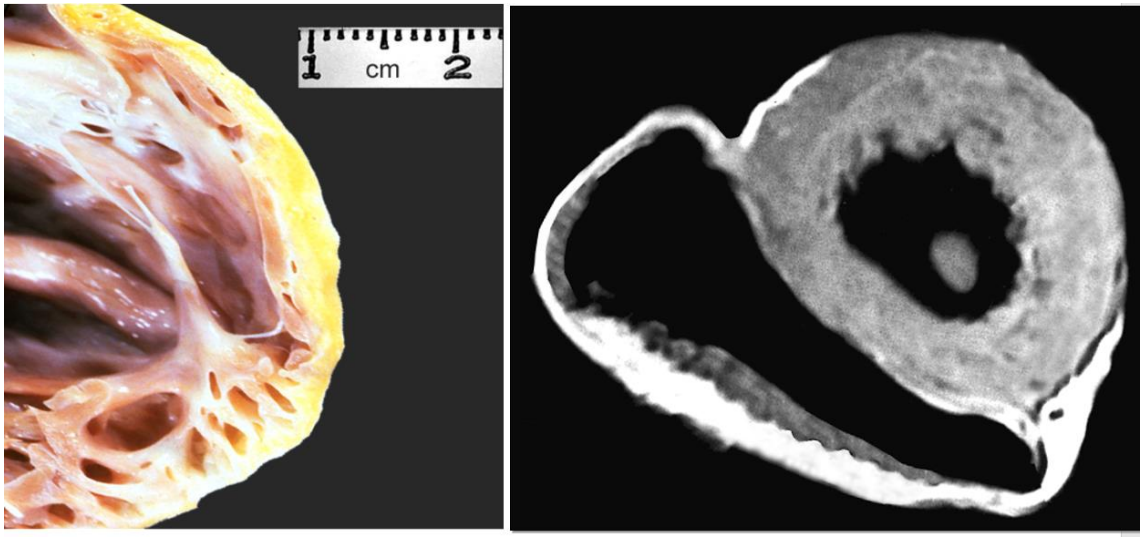
By Contrast-enhanced Cardiac Magnetic Resonance (CE-CMR):

- Major: Transmural LGE (strain pattern) of ≥1 RV region(s) (inlet, outlet, and apex in two orthogonal views).

By EMB (limited indications):

- Major: Epicardial fibrous replacement of the myocardium in ≥1 sample, with or without fatty tissue. Figure x

Figure x ARVC: Epicardial fibrofatty replacement

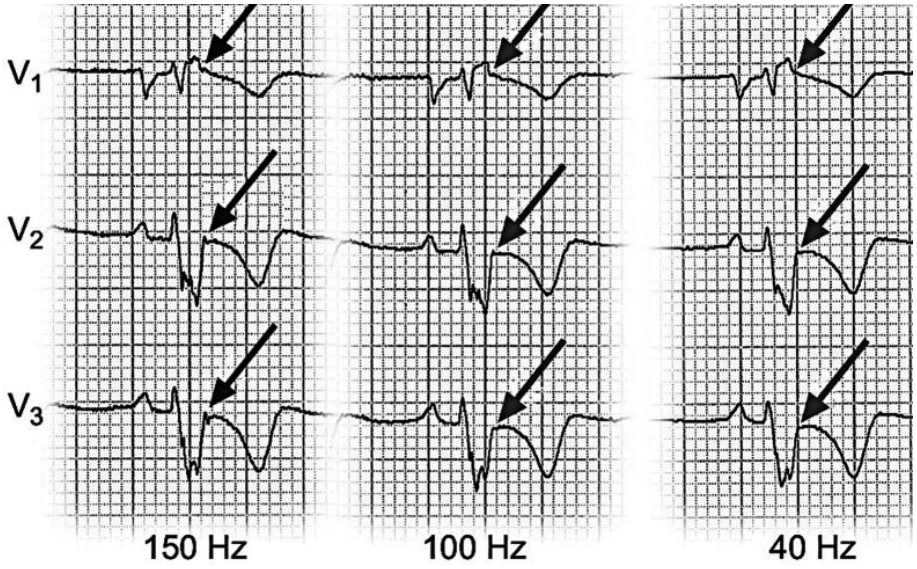


The characteristic fibrofatty replacement of RV myocardium in subepicardial layers.

V. ***Depolarization abnormalities***

- Minor: ε wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3). Epsilon wave was considered to be a major criterion for diagnosis by the 2010 Task Force for ACM diagnosis.[65] Padua diagnostic criteria for ACM, ε waves from V1 to V4 leads are classified as a minor ECG criterion because diagnostic value of the ε wave related its identification and interpretation are significantly influenced by ECG filtering and sampling rate, with unacceptable linterobserver variability.[147]

  Figure x



ε wave only observed with 150 Hz filter. Low-pass filter cutoff frequency influences the detection of the ε wave in ACM: at the recommended 150 Hz cutoff frequency, the ε wave is detected in

leads V1-V3. At a 100 Hz cutoff frequency, the ε wave is attenuated in V1-V2 and absent in V3. At 40 Hz, the ε wave disappears from leads V1-V3 (modified from ref.[148]).

- Prolonged terminal activation duration delay (TAD) of QRS ≥55 ms in V1–V3 measured from the nadir of the S wave to the end of the QRS, including R', in V1, V2, or V3 in the absence of CRBBB. The ECG pattern of a QRS delayed S wave upstroke e with TAD ≥55 ms in right precordial leads mainly if followed by TWI. Figure x

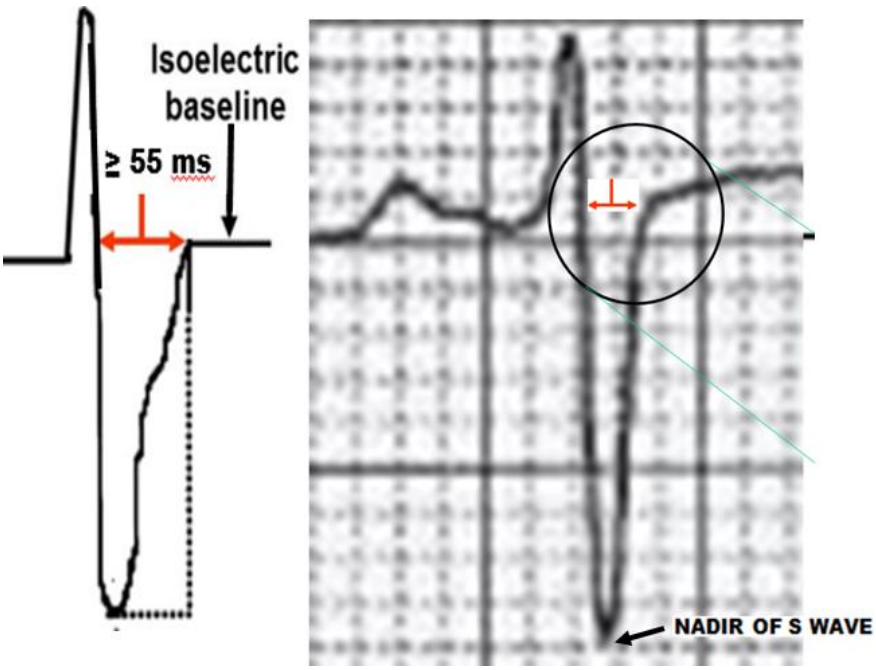


Figure. Electrocardiographic TAD of QRS ≥55 ms.

TAD is caused by desmosomal mutations, electric uncoupling, fibrofatty and fibrosis with consequent dromotropic disturbance on RVOT.[149]

- Localized prolongation (≥110 ms) of QRS complex in V1–V3.[150]

VI. ***Repolarization abnormalities***

Major: Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals with complete pubertal development (in the absence of complete RBBB). Example in next figure x

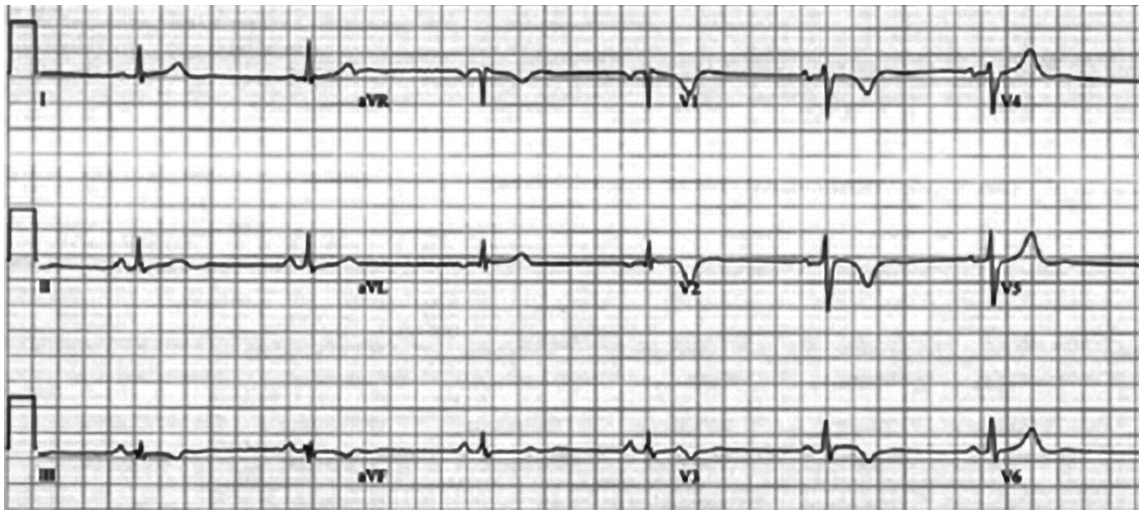


Figure. Inverted T waves in right precordial leads V1, V2, and V3 in a patient with ACM.

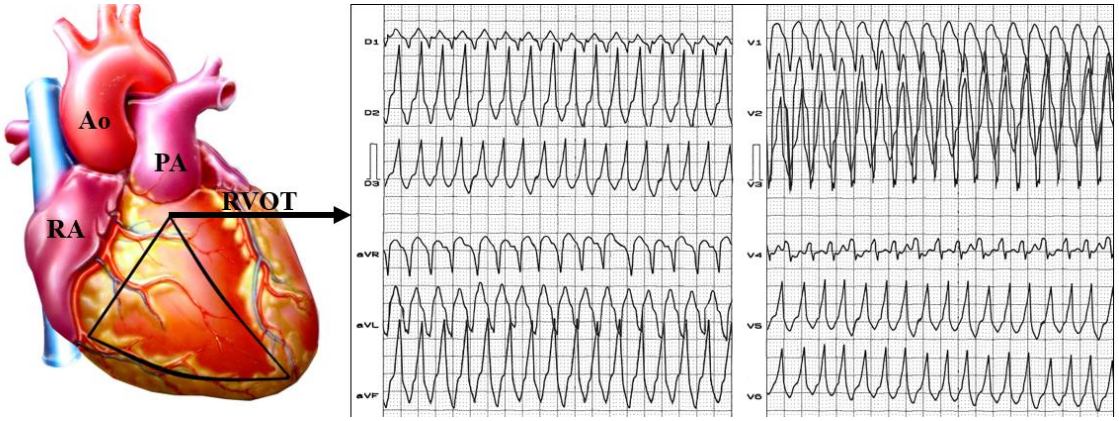
Minor: TWI in leads V1 V2 and V3 in individuals with completed pubertal development (in the absence of complete RBBB).

VII. ***Ventricular arrhythmias***

Major: Frequent PVCs (>500 per 24 hours), NS-VT or S-VT of LBBB morphology; VT with LBBB morphology and axis of -30° to -150°. Spontaneous induced during EPS No. of different VT morphologies.

Minor: Frequent PVCs (>500 per 24 hours), NS-VT or S-VT of LBBB morphology with inferior axis (“RVOT pattern”).[151, 152]

Examples



SMVT with CRBBB pattern and inferior axis in the frontal plane: positive complexes in inferior leads and negative in aVL and aVR. In this case, SÂQRS is located at the right of +90º, thus indicating origin in the RVOT. SÂQRS is between +90º and +120º ("QS" type QRS in I).

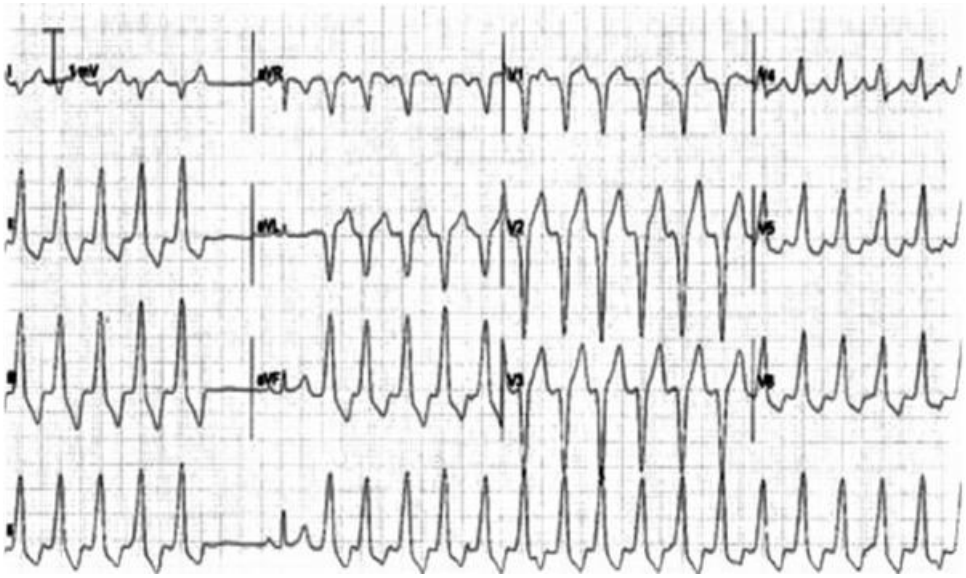


Figure. 12-lead ECG of a 36-year-old pregnant woman admitted with a 4-week history of increasingly intrusive palpitations associated with presyncope. Bursts of broad complex VT are seen with a LBBB morphology, inferior axis (right) with tall R waves in leads II, III, and aVF and precordial transition at V4 consistent with origin from the RVOT[153] (with permission).

VIII. ***Family history/genetics***

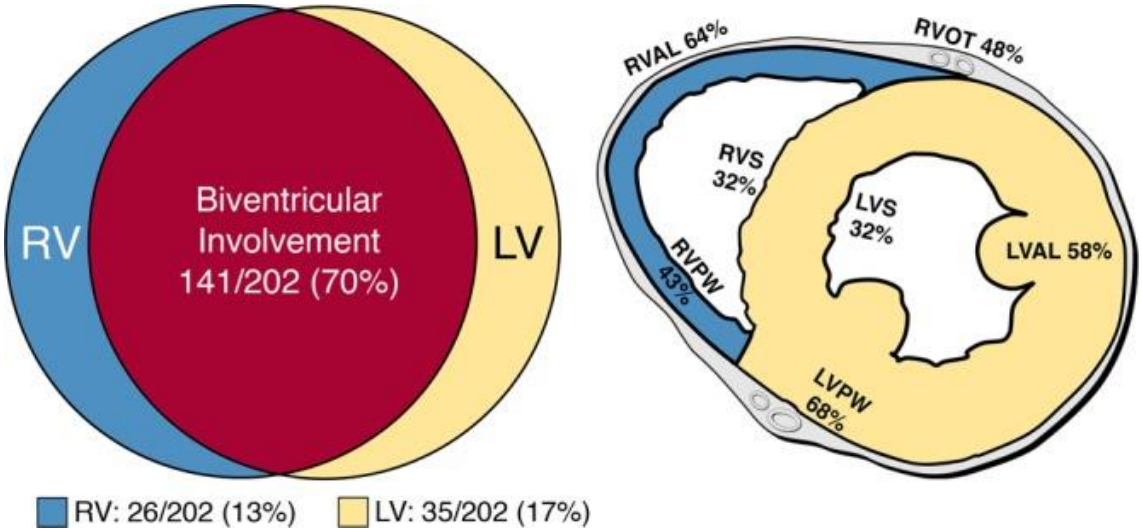
Major: ACM confirmed in a first-degree relative who meets diagnostic criteria; ACM confirmed pathologically at autopsy or surgery in a first-degree relative; identification of a pathogenic or likely pathogenesis; ACM mutation in the patient under evaluation.

Minor: history of ACM in a first-degree relative in whom it is not possible or practical to determine whether the family member meets diagnostic criteria; premature SCD (<35 years of age) due to suspected ACM in a first-degree relative; ACM confirmed pathologically or by diagnostic criteria in second-degree relative.

B. Biventricular ACM: right and left involvement

I) **Common Pathways:** Cytoskeleton, Sarcoplasmic Reticulum, Sarcomere, Ion Channel, mitochondria.

II) **Genetic Variant:** PLN gene Protein Phospholamban. Phospholamban (PLN) plays a role in cardiomyocyte calcium handling as primary inhibitor of sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA). The p.(Arg14del) pathogenic variant in the *PLN* gene results in a high risk of developing dilated or ACM with CHF. There is no established treatment other than standard CHF therapy or heart transplantation.[154]



Distribution and location of disease involvement in ACM. Left, Ventricular disease involvement among all ACM decedents (n=202) **Right**, Distribution of fibrofatty infiltration among whole hearts referred to pathology center (n=120). ACM, arrhythmogenic cardiomyopathy; LV, left ventricle; LVAL, LV anterolateral wall; LVPW, LV posterior wall; LVS, LV septum; RV, right ventricle; RVAL, RV anterolateral wall; RVOT, RV outflow tract; RVPW, RV posterior wall; and RVS, RV septum.[155]

The 2010 Task Force criteria may fail to diagnose biventricular ACM before death. In a large autopsy study, Miles et al. demonstrate that LV involvement is observed in most decedents with ACM and the LV is exclusively involved in nearly a fifth of cases. Age at death, sex, normal macroscopic appearance of the heart, and participation in competitive sport were not associated with the presence of LV involvement. The authors described diagnostic histopathologic criteria for ACM involving either or both ventricles. This study identified that the heart was macroscopically normal in 20% of decedents with ACM; expert pathological assessment, including histology, is therefore crucial to inform diagnosis in cases of initially unexplained SCD. LV variants of ACM may evade clinical detection

using current diagnostic tools; this should be addressed revisions of 2010 Task Force criteria

C. LV Dominant left ALVC Left-dominant arrhythmogenic cardiomyopathy (LDAC) (New diagnostic criteria) or Arrhythmogenic Left Ventricular Cardiomyopathy

Left-dominant ACM is a subtype of arrhythmogenic ventricular cardiomyopathy characterized by early predominant LV involvement defined as a LV isolated LGE and fibro-fatty replacement at CMRI plus genetic variants associated with ARVC and of an EMB showing fibro-fatty replacement complying with the 2010 International Task Force Criteria in the LV. Clinical data regarding patients with arrhythmogenic left ventricular cardiomyopathy are limited, and this phenotype is yet to be completely described. The arrhythmogenic LV cardiomyopathy phenotype is characterized by a disease involvement of the laterobasal area of the LV.

I) **Common Pathways:** Cytoskeleton, sarcoplasmic reticulum, sarcomere, ion channel, mitochondria,

II) **Genetic Variants:** *Lamin* A/C gene *(LMNA), DSP (DS*= variants are more likely to be associated with LV dysfunction.[38, 94]*, TMEM43, LDB3, Desmin, α-actin, BAG3, NKX2-5, RBM20, SCN5A, KCNQ1, KCNH2, TRPM4, DSP Mitochondrial mutations.* Positive genetic testing for pathogenic (class V)/likely pathogenic (class IV) variants associated with ARVC with LV involvement (namely: desmoplakin [*DSP*], desmoglein-2 [*DSG2*], desmocollin-2 [*DSC-2*], and plakoglobin [*JUP*]).[49]

Lamin A/C (LMNA) cardiomyopathy forms an important and increasingly recognized group within the broad spectrum of non-ischemic cardiomyopathies. LMNA cardiomyopathy typically presents with atrioventricular block followed by recurrent ventricular arrhythmias with a high tendency to progression to end stage CHF. Lamin A/C gene mutations can be found in severe forms of ARVC. Dilated cardiomyopathy caused by lamin A/C gene (LMNA) mutation is complicated with atrioventricular (AV) conduction disturbances, malignant ventricular arrhythmias, and progressive severe CHF. Lamin A/C gene should be added to desmosomal genes when genetically testing patients with suspected ARVC, particularly when they also have ECG evidence for conduction disease.[127]

DSP

III) **Morph-functional ventricular abnormalities**

By echocardiography, CMR or angiography:

Minor: global LV systolic dysfunction (depression of LV EF according to the imaging test monograms for age and sex, and BSA or reduction of echocardiographic global longitudinal strain), with or without LV dilatation (increase of LV EDV according to the imaging test specific monograms for age, sex, and BSA).

Minor: regional LV hypokinesia or akinesia of LV free wall, septum, or both.

IV) **Structural myocardial abnormalities**

By Contrast-enhanced Cardiac Magnetic Resonance (CE-CMR):

Major: LV LGE (strain pattern) of ≥1 Bull's Eye segment(s) (in 2 orthogonal views) of the free wall (subepicardial or midmyocardial), septum, or both (excluding septal junctional LGE).

V) **Depolarization abnormalities**

- Low QRS voltages (<0.5 mV peak to peak) in limb leads (in the absence of obesity, emphysema, or pericardial effusion) It is caused by decrease of LV myocardial mass by fibro-fatty replacement.[156-160] Example

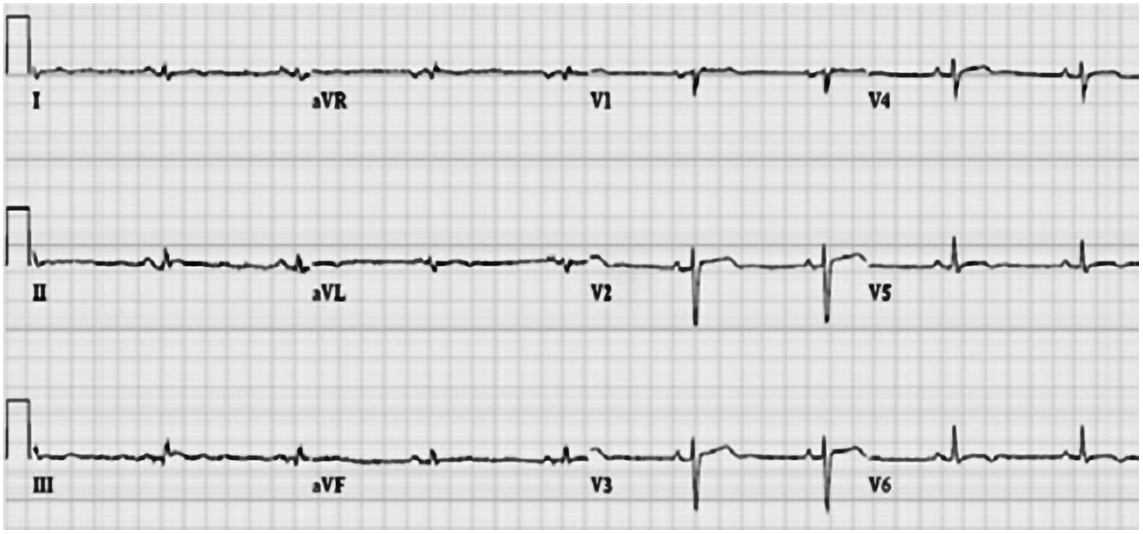
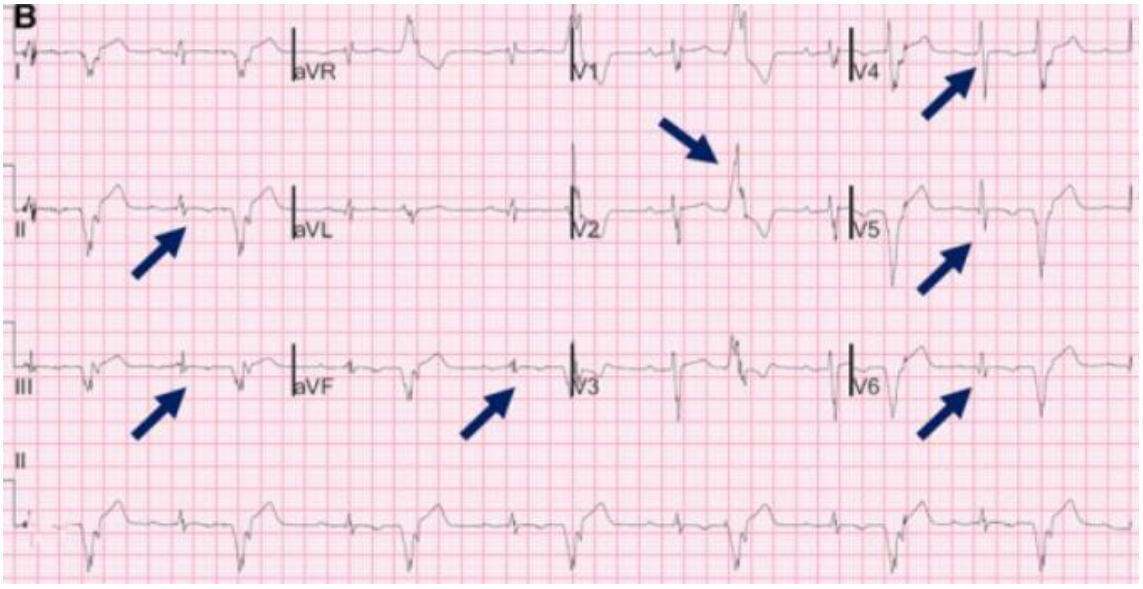


Figure. 12-lead ECG with sinus rhythm. Outstanding low QRS voltages (low QRS voltages <0.5 mV peak to peak in limb leads) and negative T waves in leads V5 -V6 in a patient with ALVC.



B, 12-lead ECG showing first-degree AV block, inferolateral TWI (arrows), and low-voltage limb lead QRS complexes, prolonged terminal activation duration in V1, and ventricular bigeminy with fragmented, broad, PVCs of RBBB morphology and superior axis (arrow).

VI) **Repolarization abnormalities**

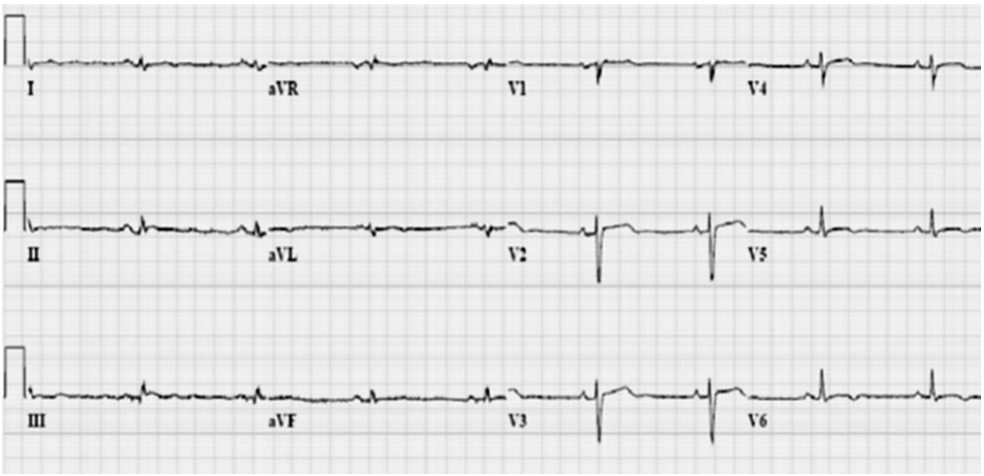
- Minor: TWI in V4-V6 in the absence of complete LBBB, The ECG reveal repolarization abnormalities at inferolateral leads in the absence of diagnostic structural/functional alterations or obstructive CAD. The most commonly involved peripheral and precordial leads were I, aVL, aVF, and V_5 and V_6, respectively; frequent morbid association of ventricular arrhythmias and unexplained inferolateral TWI.[161]

Clinical features of Left-Dominant Arrhythmogenic Cardiomyopathy (LDAC)

1. Low QRS voltage (<0.5 mV) in limb leads is frequent in ALVC. Low QRS voltages in limb leads indicate the presence of late gadolinium

enhancement/myocardial fibrosis of the LV wall. The electrocardiographic pattern of low QRS voltages in limb leads, which was shown to be a more accurate predictor of left ventricular involvement than T-wave inversion in the inferolateral leads, should be included among the 2010 International Task Force criteria for diagnosis of biventricular arrhythmogenic cardiomyopathy.[157]

1. Unexplained ventricular arrhythmia of RBBB pattern. In patients with complete RBBB and ACM, fQRS is more prevalent in comparison with other patients with CRBBB. Additionally, patients who develop CRBBB often have biventricular HF in follow up.[162]
2. Unexplained TWI in inferior or lateral leads. This is the most common ECG finding is unexplained TWI or flattened in in the left-lateral leads I, aVL, V5-V6 and in the inferior leads II, III and aVF: inferolateral TWI[163] in the absence of diagnostic structural/functional alterations or obstructive coronary artery disease.[161]
3. Positive T-waves in aVR or with T-wave minimally positive. Examples



12-lead ECG during normal sinus rhythm. Outstanding are the low voltages (voltages <0.5 mV in standard leads) and negative T waves in leads V5 -V6 in a patient with ALVC.

Figure x shows a typical example of **LDAC ECG**

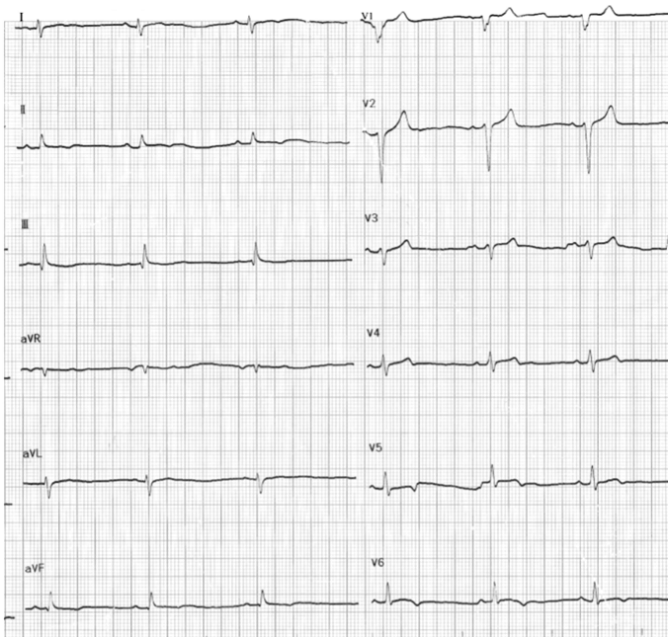
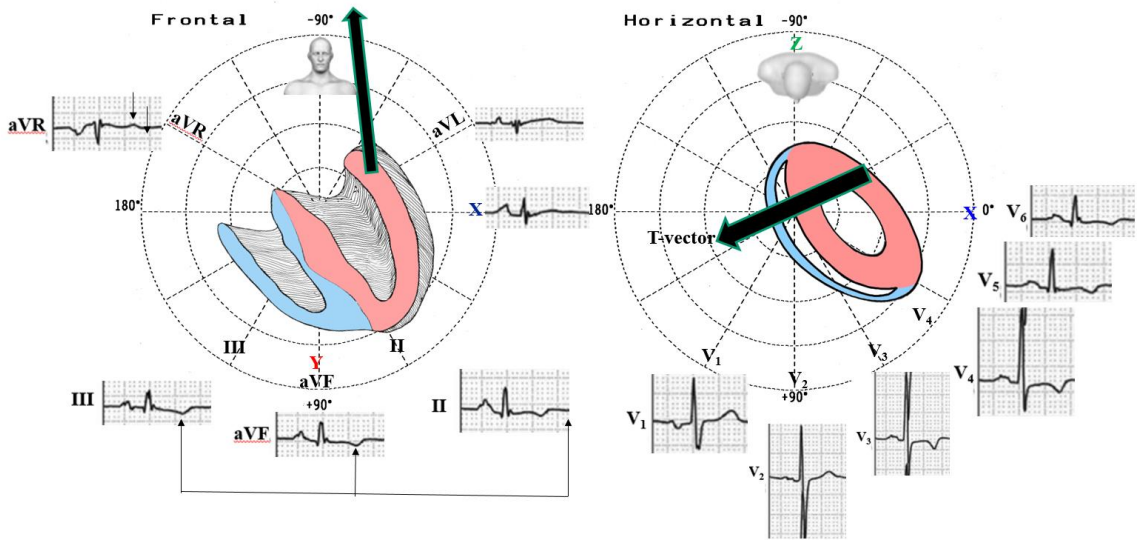
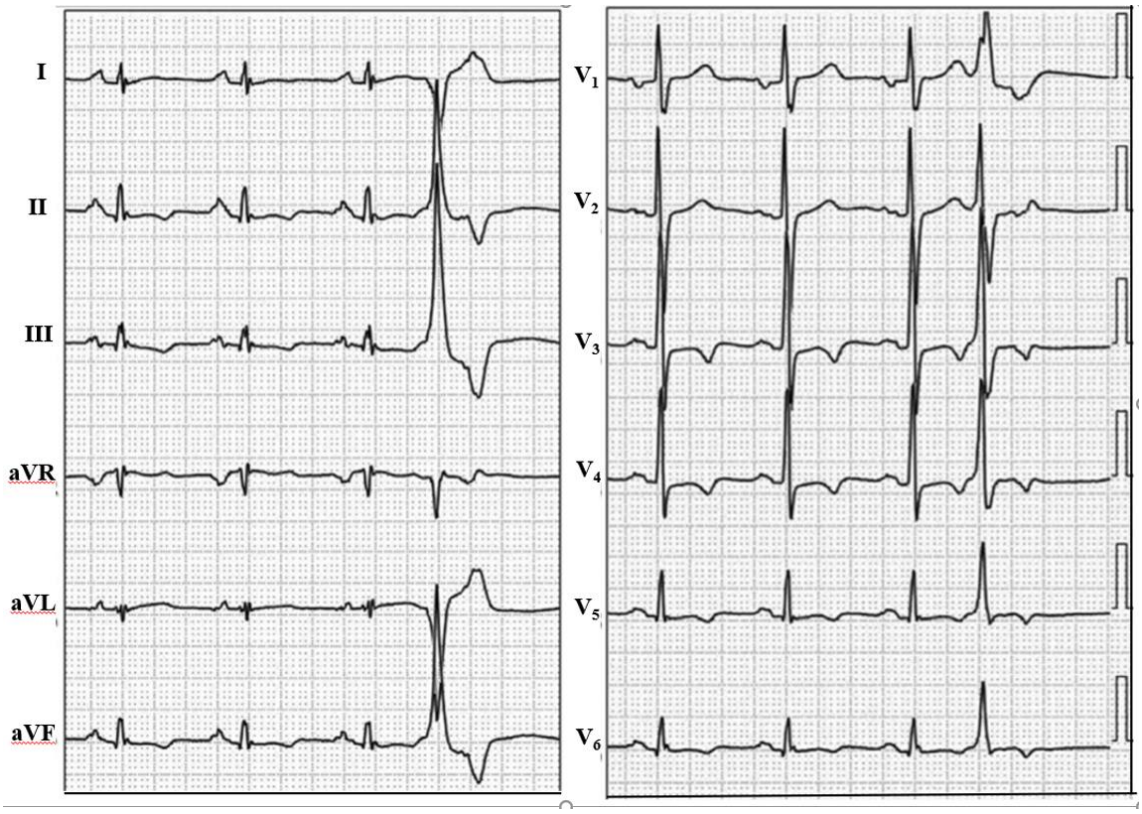


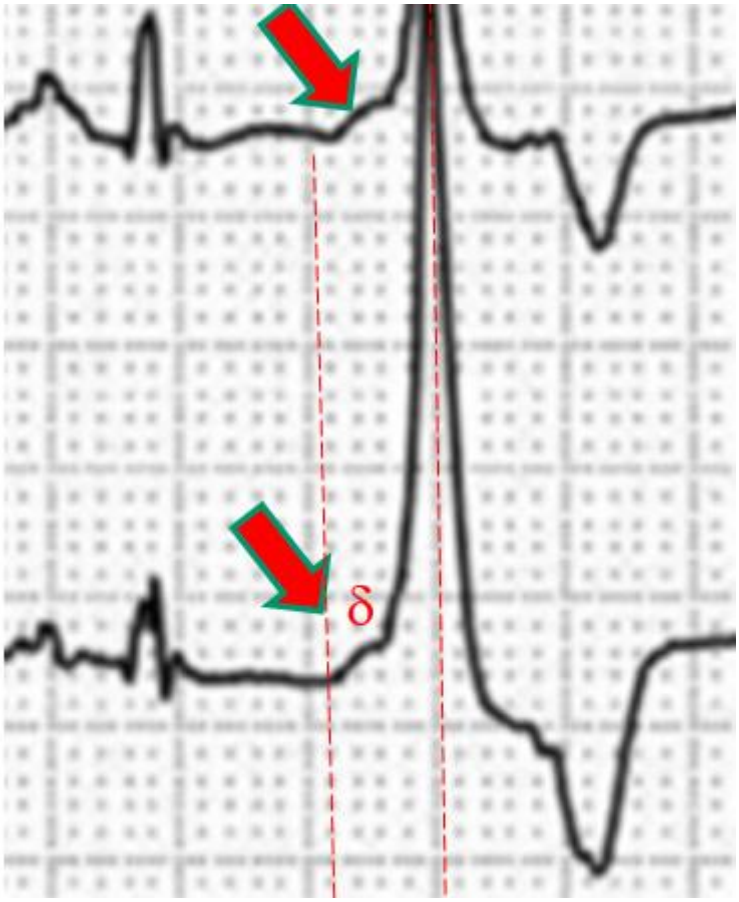
Fig. x. 12-lead ECG recording (25 mm/s, 10 mm/mV). There is low QRS voltage in limb and left lateral precordial leads, TWI in lateral leads V5 and V6, and flattening T waves in leads II, III and aVF; fragmented QRS complex(fQRS) is registered in lead V1.

Left-dominant arrhythmogenic cardiomyopathy (ALVC): T-wave polarity



ECG showing TWI in the left-sided leads and a PVCs of LV origin





"Wolffian extrasystoles" PVCs from the base of the ventricles (arrows)

Very prolonged R-Wave Peak- Time (RWPT) or intrisecoid deflection >80 ms (160 ms)

4. Mild LV dilation and/or in “classical” ARVC/D. Evidence of RV parietal block is manifest by a QRS duration in V1 ≥110 msec and a longer QRS duration in the right then left precordial leads.[164]
5. LV systolic impairment.
6. Myocyte loss with fibrofatty or fibrotic replacement confirmed by an EMB sample obtained from the LV in one of the areas presenting LGE in the LV on CMRI, according to the existing 2010 ITFC major criteria definition.[156, 157, 165] Presence of fibrous

AND fatty infiltration on an endomyocardial biopsy (EMB) sample obtained from the LV in one of the areas presenting LGE at CMR, according to the existing 2010 ITFC major criteria definition for the RV.

7. Exclusion criteria: Patients without genetic testing, clinical suspicion of cardiac sarcoidosis due to initial radiological/clinical findings, or with a history of a recent (<3 months) infection at the time of CMRI, to reduce the risk of including phenocopies. Patients with a positive family history up to 3 generations of any cardiomyopathy other than ACM and endurance athletes (defined as per training regime >6 h/wk of practicing sports with a moderate to intense dynamic component and any athlete practicing sports at a professional level).

VII) **Ventricular arrhythmias:**

- Minor: frequent PVCs (>500 per 24 hours), NS-VT or S-VT with a RBBB type (excluding the “fascicular pattern”) PVCs with a QRS complex of the RBBB type and superior axis. Figure X

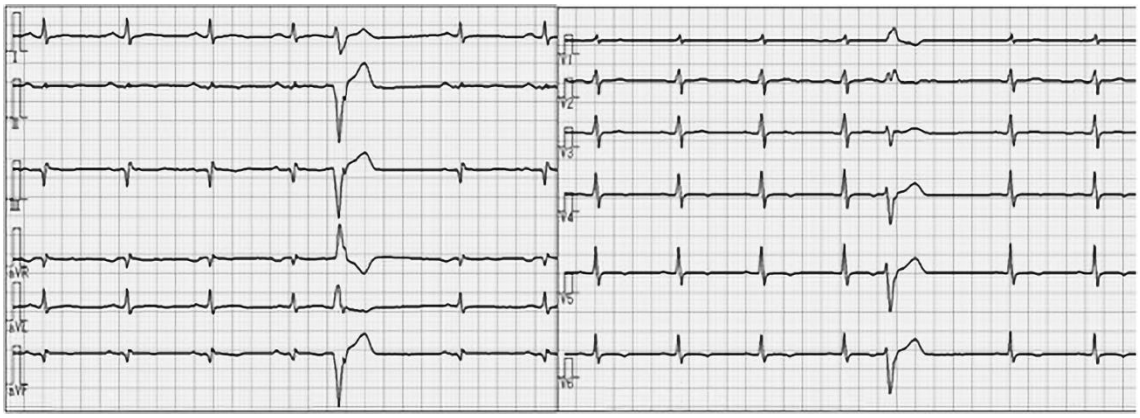
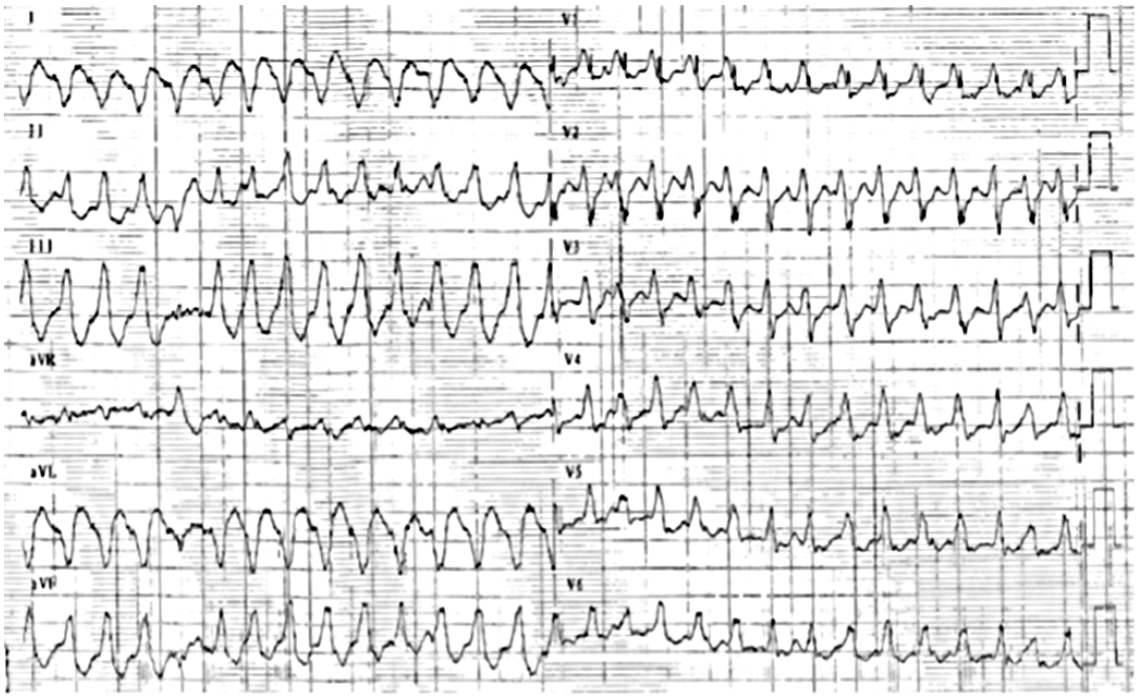


Figure. 12-lead ECG: sinus rhythm. heart rate of 68 bpm, low QRS amplitude in the limb leads, and flat or inverted T waves in the inferolateral leads. PVC with a

QRS complex of the RBBB pattern with superior axis and prolonged R-wave peak time in V_1 suggested that the epicardial basal LV may be the origin of PVC.[166]

A 74-year-old man had abnormal LV function. His ECG is showed below.

Which is the diagnosis? Clinical genetic diagnosis**:** Left-dominant arrhythmogenic cardiomyopathy with a nonsense mutation in *DSP.*[167]



12-lead ECG recording (while off drugs) of monomorphic VT with RBBB morphology, right axis deviation, and cycle length of 350 ms in a patient with ALVC.

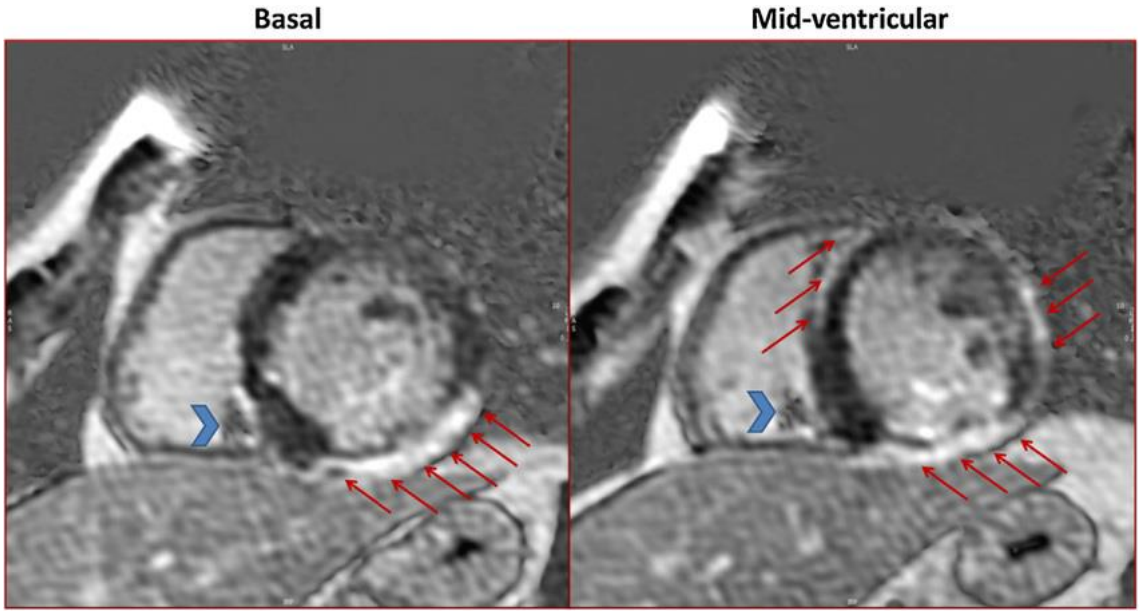
TTE: systolic dysfunction of the LV Low LVEF

Cardiac computed tomography imaging revealed banded and patchy densities observed frequently from the middle to epicardial layer of the LV wall.

CMRI: fat signals on fat-selective images and LGE in the mid-wall to subepicardial layers in the LV myocardium. Presence of a subepicardial LGE

pattern with nonischemic distribution and fatty infiltration at CMRI affecting exclusively the LV.

Figure



CMRI showing a subepicardial enhancement pattern on the LGE images (arrows). The extensive amount of enhancement and the absence of inflammatory activity are indicative of ALVC.

Invasive evaluation, an EVM-guided EMB from the LV performed to confirm diagnosis.[168]

EMB: presence of fibrofatty replacement observed of LV lateral wall.[144]

EMB in the diagnosis and treatment of cardiovascular diseases remains a controversial issue, especially in the setting of unexplained ventricular arrhythmias. Electroanatomic voltage mapping (EMB) represents an important additional diagnostic test for cardiomyopathies when uncertainties remain after non-invasive evaluation. EMB guided by EVM reached a diagnostic yield as high as 74.1%. EMB proved to be a useful tool in the clinical management of patients,

as it allowed to correctly reclassify a significant number of patients who would have been misdiagnosed based only on non-invasive assessment.

Genetic analysis: performed with Next Generation Sequencing. Nonsense mutation in the desmoplakin gene. ***DSP***

Differential diagnosis of LDAC

1) **With dilated cardiomyopathy (DCM):** LDACM is differentiated from DCM since most patients have a normal or near-normal LVEF but a high arrhythmic profile, while in DCM, LV impairment precedes the arrhythmogenic disease state
2) **With myocarditis:** Differential diagnosis from myocarditis is challenging, since most of the ECG, echocardiographic and CMR findings overlap. Hot phases of LDAC present with chest pain and troponin rise, mimicking acute viral myocarditis.[169] and inflammatory infiltrates, presenting as patchy myocarditis, is frequent finding in LDAC.[1] **Autopsy features:** Histopathological affecting predominantly the LV at subepicardial/midwall myocardial layers.

ACM: arrhythmogenic cardiomyopathy; BSA: body surface area; EDV: end diastolic volume; EF: ejection fraction; ITF: International Task Force; LBBB: left bundle branch block; LGE: late gadolinium enhancement; LV: left ventricle; RBBB: right bundle branch block; RV: right ventricle; RVOT: right ventricular outflow tract.

High risk factors in ACM

- Positive history of CHF (independent risk predictor);
- CHF and the presence of LV involvement (independent risk predictor);[170]
- LA dilatation;
- Prolonged PR interval;
- QRSd > in V1;
- Presence of bundle branch block;
- LV involvement;
- History of VT;
- After adjustment for sex, history of syncope, chest pain, inaugural VT, recurrence of VT, and QRS dispersion, clinical signs of RV failure and LV dysfunction both remained independently associated with cardiovascular mortality. The combined presence of one of these risk factors and VT identifies high-risk subjects for cardiovascular mortality, whereas patients without VT displayed the best prognosis;[171]
- QRS dispersion, history of syncope and right and/or left ventricular abnormalities at radionuclide angiography proved to be independent noninvasive predictors of sudden death.[172]

Family history /genetic background

Complains manifestations

Electrocardiography: depolarization and repolarization finding,

Functional and structural ventricular abnormalities, tissue characterization findings,

Modified protocol to obtain the ECG in patients with suspicion of ACM

The tracing should run at a double velocity (50 mm/s) and double voltage (20 mm/s) to compare the duration of QRS complexes (QRSd) in different leads, as well as to try to record Epsilon waves.

The Fontaine bipolar precordial leads

Fontaine bipolar precordial leads (F-ECG) are used to increase the sensitivity of epsilon wave detection. The tracing should be obtained from I and aVF at double velocity and amplitude, placing the electrode of the left arm on the xiphoid appendix, the one from the right arm on the manubrium sternum, and the one from the left leg on the rib at the fourth or fifth space with the aim of improving the ability to detect Epsilon waves.

The Fontaine bipolar precordial leads are placed at the manubrium of sternum, xiphoid, and V4 positions using the right arm connection, left arm connection, and left foot connection, respectively.

Epsilon waves are detected by: Standard 12-lead electrocardiography (S-ECG), right-sided precordial lead electrocardiography (R-ECG), Fontaine bipolar precordial lead electrocardiography (F-ECG).

The detection rate using combined methods is significantly higher than that by S-ECG alone.

Fontaine bipolar precordial leads have the best sensitivity among the three options. The placement of the foot lead (positive) in position V4 provides, instead of regular leads I, II, and III, three bipolar chest leads that can be called FI, FII, and FIII. Tracings are then produced by setting the machine on regular leads I, II, and III. This arrangement is used to record specifically the potentials developed

in the RV, from the RVOT to the diaphragmatic area. The vertical bipolar lead FI (similar to the aVF lead) seems to be the most appropriate to record epsilon waves; FI also magnifies the atrial potentials. As late potentials were supposed to be the result of late activation of a limited group of fibers, the term “post-excitation” looked logical, since it was observed after the main excitation of the ventricle, leading to the QRS complex (Figure X).

The term “epsilon” was appropriate because it occurs in the Greek alphabet after delta; thus, delta represents the preexcitation and epsilon the post-excitation phenomenon.[173]

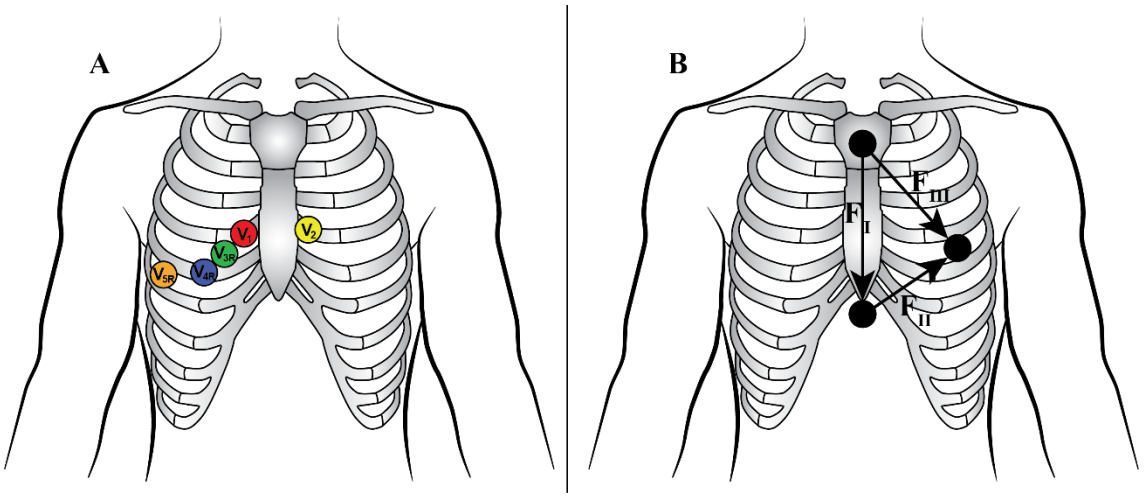


Figure. A) Right precordial leads. B) Fontaine bipolar precordial leads.

Leads are placed as shown Right Arm (**RA**) over the manubrium; Left Arm (**LA**) over the xiphoid process; and Left Leg (**LL**) in the standard V4 position (5th ICS MCL). Instead of regular leads I, II, and III, there are now three *bipolar* chest leads that are termed FI, FII, and FIII. These record potentials developed in the RV, from the infundibulum to the diaphragm. The vertical bipolar lead FI (similar to aVF) magnifies the atrial potentials and can be used to record:

- Epsilon waves
- Search for AV dissociation in ventricular tachycardia

- Study abnormal atrial rhythms when the P waves are too small on regular leads

Electrocardiographic features in ACM

Approximately 90% of patients with ACM present ECG anomalies. ACM diagnosis may be excluded if the ECG is normal six years after the VT episode.[174]

Usually sinus rhythm; however, there is a report of the case of a 60-year-old male patient with ACM, who developed sick sinus syndrome (sinoatrial node with recovery time of 6113 ms). The authors explained the cause of atrial arrhythmia by gradual reposition of right atrial myocytes by fatty tissue.[175]

There is a description of giant P wave associated with QRS complex of low amplitude, in patients with ACM.[176] Rest ECG with RVH and significant increase of QRS complex dispersion of 47.1±18.9 ms are observed in cases of CHF. Biatrial enlargement and reduction of QRS dispersion of 33.0±23.1 ms are also observed in cases of biventricular CHF.[177]

PR interval prolongation has been described,[178] which is a predictor of adverse results in patients with ACM.

Abnormalities in depolarization and repolarization in ECG are common in cases of ACM.

ECG abnormalities in depolarization/conduction

Prolongation of QRS complex (110 ms) located in the right precordial leads (V1-V3) in adult patients in the absence of CRBBB (prolonged S wave upstroke) from V1 to V3. QRS with 55 ms is the most prevalent characteristic of the ECG (95% of cases) and is correlated with the severity of the disease and induction of VT in programmed ventricular stimulation (PVS). Prolongation in S wave duration

in the anteroseptal leads in the ECG (V1-V3) is a significant marker for ACM diagnosis.

Automated medication in S wave duration (Marquette Mac12, Mac15 or MacVue) in leads V1-V3 of the surface ECG was conducted in 141 healthy children between 5 and 15 years old (9.6 ± 2.7 years old) and they were compared to 27 pediatric patients with ACM. Available ECGs were assessed in the initial and final phase in patients with ACM, obtained respectively at ages of 11.6 ± 3.9 and 14.3 ± 3.4 years. ACM was diagnosed in children with VT and CLBBB morphology, using diagnostic criteria already published for adult patients with ACM or who had typical findings in biopsy.

The result from the summation of the QRS complexes duration from V1 to V3 is divided by the summation of the QRS complexes duration from V4 to V6 $\left({}^{V1+V2+V3}/_{V4+V5+V6}\right)$. When this equation results in a value ≥1.2, it constitutes a sign of high sensitivity for ACM diagnosis, since it is present in 98% of patients with this cardiomyopathy. A research showed that this sign is not specific for ACM because it has been also observed in BrS. This longer duration of QRS complexes in the right precordial leads is due to the so-called right parietal block, a characteristic of ACM. Possibly QRS complexes may be of low voltage, which is observed when the disease is diffuse or there is participation with the conduction system.[179]

There is evidence of peripheral right branch blocks in ACM, as the author Guy Fontaine proved some time ago: topographic incomplete or complete RBBB occurs in the fascicular portion of the right branch and/or in the RV free wall after the trunk of the branch splits at the base of the papillary muscle of the tricuspid valve, and this mechanism seems to be due to the participation of dysplasia in

the free wall, in the RVOT, RVIT or the apical region (triangle of dysplasia), where the dysplasia is found.[180]

Pattern of complete RBBB[65 173 181] (15% of cases), incomplete RBBB or right end conduction delay (18% of cases).

Alterations of repolarization

ST segment elevation with different morphologies is present in 25% of cases.

TWI in the right precordial leads (from V1 to V3) >12 years old, in the absence of complete RBBB.

QRSD V_1, V_2 and V_3 / QRSD V_4, V_5 and V_6 relationship

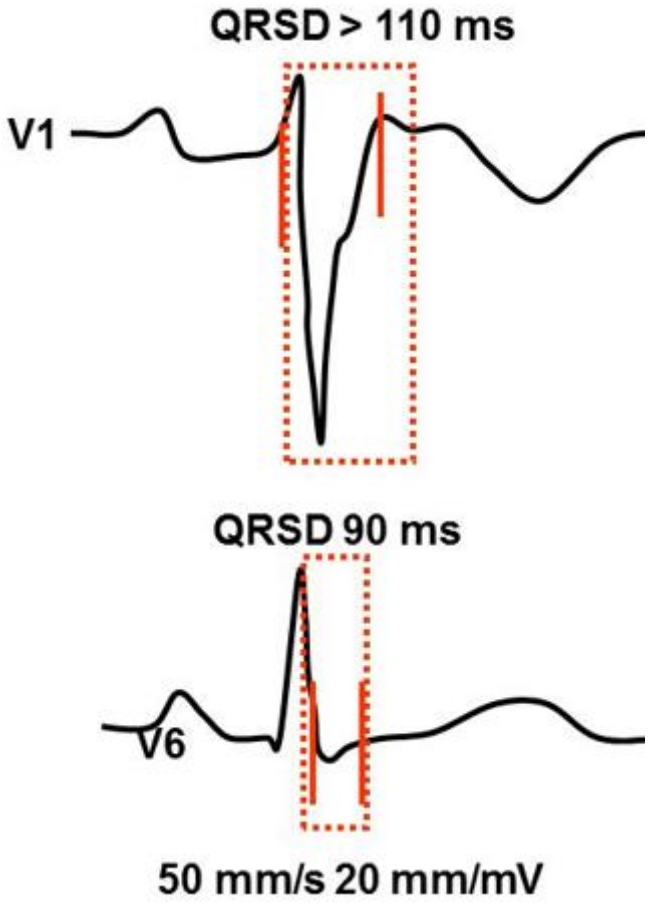


Figure. Electrocardiographic features in ACM.

QRSD of $V_1+V_2+V_3$ /V_4, V_5, V_6 ≥1.2 in approximately 65% of cases. QRS prolongation located in the right precordial leads.[145]

QRSD ≥ from V_1 to V_3 with 91% sensitivity, 90% specificity that predicts VT in patients with ACM.[182]

BrS may display prolongation in QT interval duration from V_1 to V_3 and subsequently prolongation of QTc interval in the right precordial leads.[183]

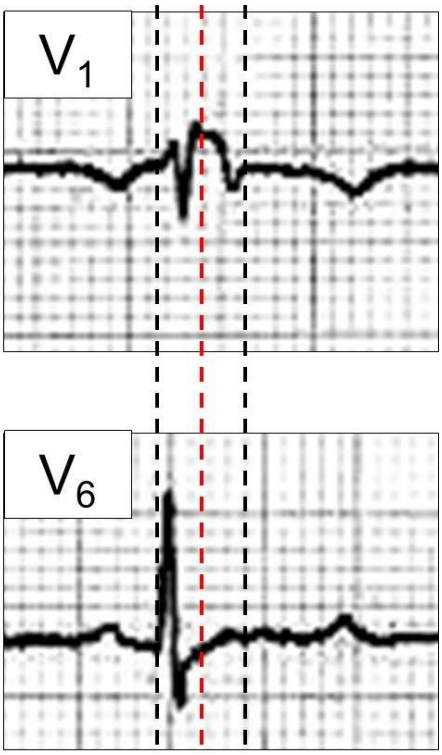


Figure. ECG tracing.

QRS duration (QRSD) in V_1 = 170 ms

QRS duration (QRSD) in V_6 = 90 ms

The mechanism of the right conduction defects is not a disease of the bundle branch itself but a distal block probably located in the RV wall. This

hypothesis is supported by the histological appearances of the dysplastic zones.[180]

Among those without RBBB, a prolonged S-wave upstroke in V1 through V3 ≥55 ms was the most prevalent ECG feature (95%) and correlated with disease severity and induction of VT on EPS. This feature also best distinguished ACM (diffuse and localized) from the RVOT.[145]

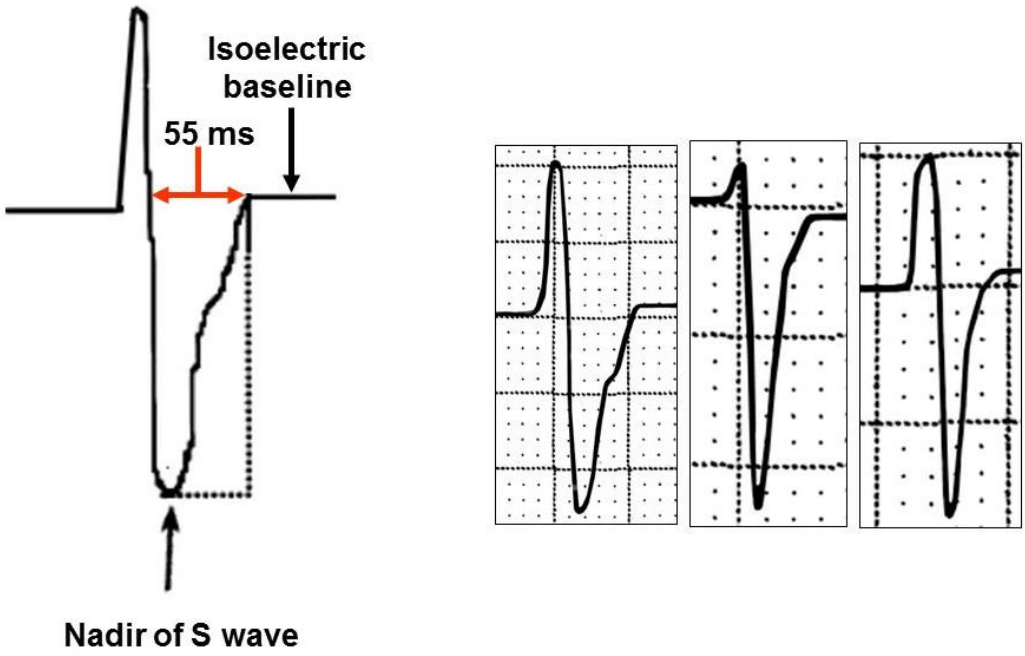


Figure. ECG tracing.

Concept of parietal block

Located prolongation has been described for QRSd interval from V1 to V3, related to V1 + V2 + V3 / V4 + V5 + V6 >1.2 in 97% of cases of ACM, and it is related with the amount of fibrotic tissue in patients with VT that originates in the RV.

The sensitivity of this criterion is not known in other entities and speaks in favor of slow RV conduction. Recent studies show that the sign is not specific, since it is found in BrS with QT interval prolongation only from V1 to V3.[183]

If QT interval prolongation occurs only from V1 to V3, it is clear that this is due to depolarization time prolongation.

If we admit that in BrS there is some degree of RBBB, this QT interval prolongation may be partially due to this fact.

QT interval is used to measure ventricular repolarization; nevertheless, this parameter includes ventricular depolarization (QRS) and represents the so-called electrical systole, which is the addition of ventricular depolarization (QRS) and repolarization (ST/T = JT interval).

If branch block or WPW ventricular preexcitation occurs, the QTc interval does not express ventricular repolarization correctly. In these cases, the JT interval measurement is more reliable (JT = QT - QRSd) than the QT interval, because the parameter excludes depolarization that is prolonged, as a consequence of sequential activation of the biventricular chamber (normally this activation is simultaneous).

The JT interval value and its limits

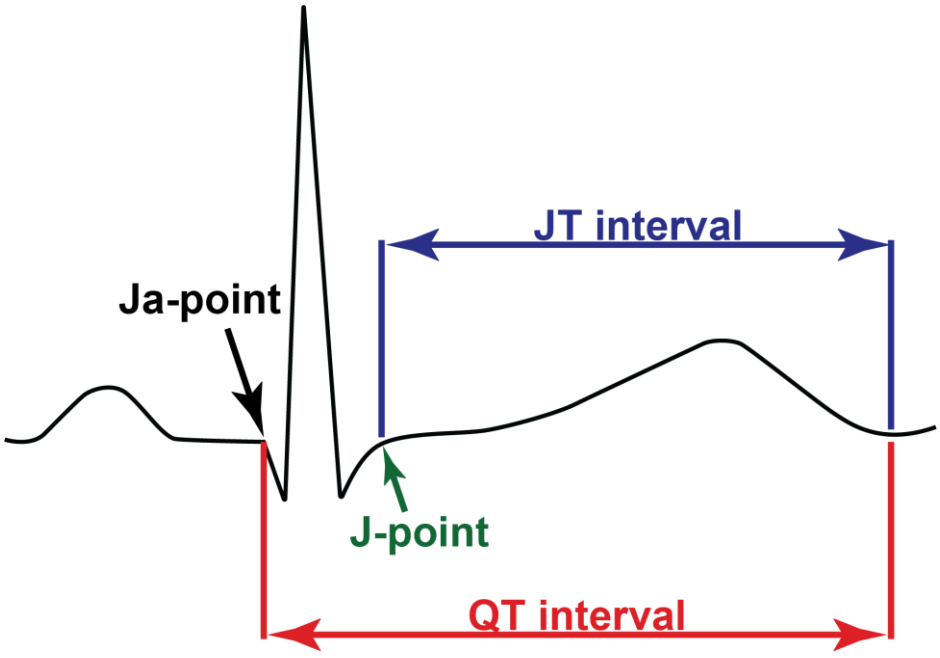


Figure. The JT interval value and its limits.

Where is the end of QRS complex (J point)?

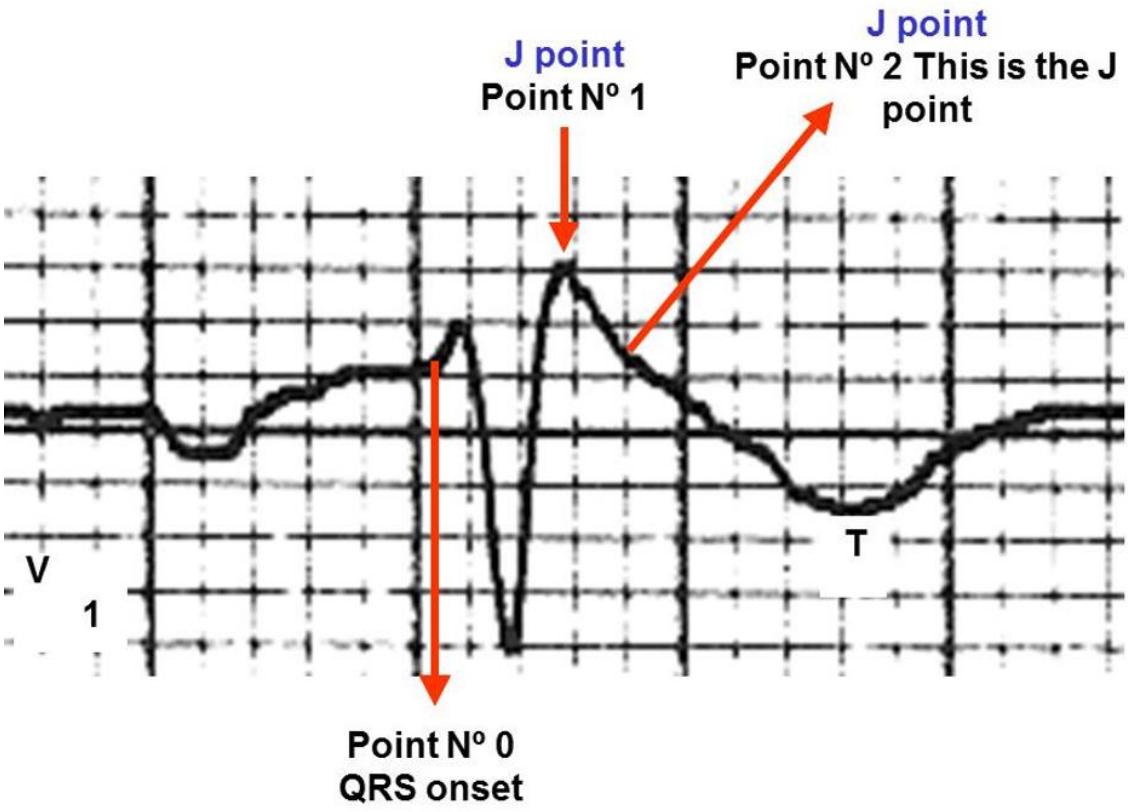


Figure. In type 1 Brugada ECG pattern and in concealed forms of ACM, it is difficult to determine accurately where the QRS complex ends and the repolarization starts; in another words, it is difficult to know the precise location of the J point.

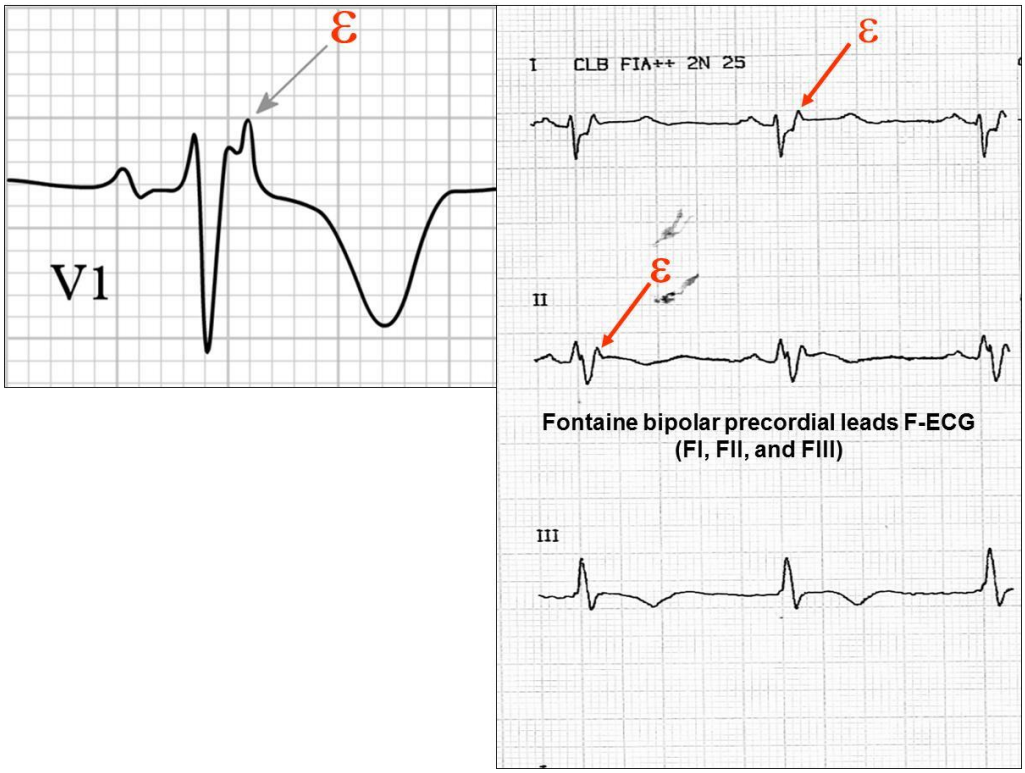


Figure. Source: ECGPEDIA.ORG.

Characteristics of epsilon or Fontaine wave in ACM

"Fontaine discovered and named the epsilon waves. He chose the epsilon because it follows delta in the Greek alphabet and is the mathematical symbol for smallness".[184]

Epsilon waves are small notches or oscillations in variable quantities (1, 2, 3 or more), located at the end of QRS, in the J point or onset of ST segment (there is no consensus about this), observed in right precordial leads; however Dr. Li Zhang et al, found the ε wave in the leads of the frontal plane, especially in inferior leads.(reference?)

The frequency of epsilon waves in ACM is approximately 15-30% of cases in 12-lead ECG or higher rate in HRECG. This percentage increases if we use the ECG with the modified protocol.

Epsilon wave was considered to be a major criterion for diagnosis by the 2010 Task Force for ACM diagnosis.[65]

In spite of the characteristics in ACM, epsilon waves are not pathognomonic, since they have been described in other diseases associated with myocardial damage: RV infarction, inferior or dorsal,[185] sarcoidosis,[186] sickle cell anemia,[184] etc.

Meaning: late posterior potentials (PP) that occur in the RV free wall in patients with ACM.

TWI in leads V1-V3 and/or ε wave are found in 70% of patients with ACM. Epicardial electrophysiological studies in dysplastic areas reveal the LP that occur at the end of the QRS complex, in the J point, and at the onset of the ST segment, are explained by fibro-fatty substitution of myocardial tissue.[180]

The simple presence of epsilon waves indicate slow and fragmented conduction, which favors reentry circuits, which in turn result in MVT runs with CLBBB morphology by originating in the RV.[187] [188]

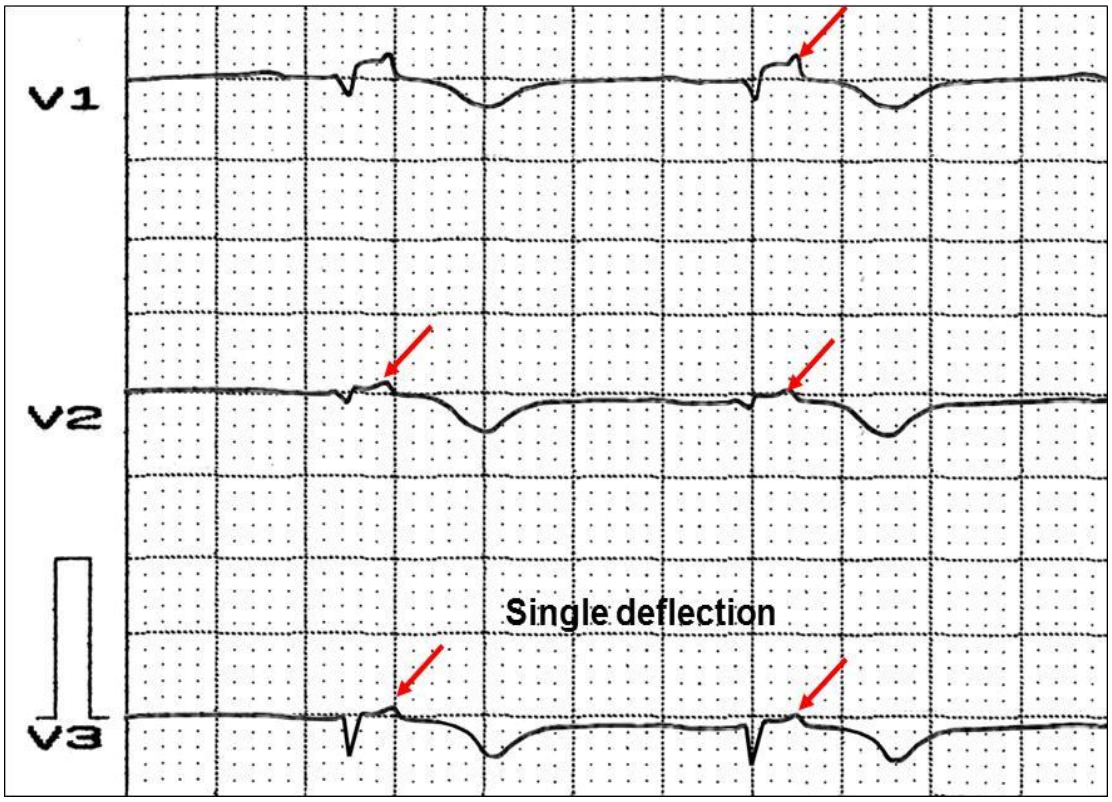


Figure. Morphological classification of epsilon wave.

Epsilon wave with multiple deflections

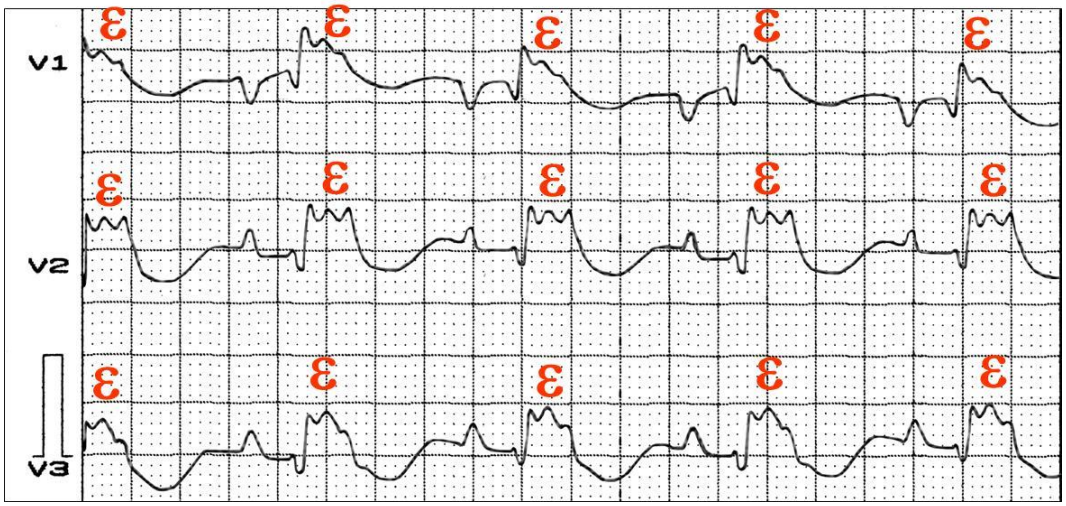


Figure. Epsilon wave characteristics in ACM.

Epsilon wave (ε) characteristics in ACM

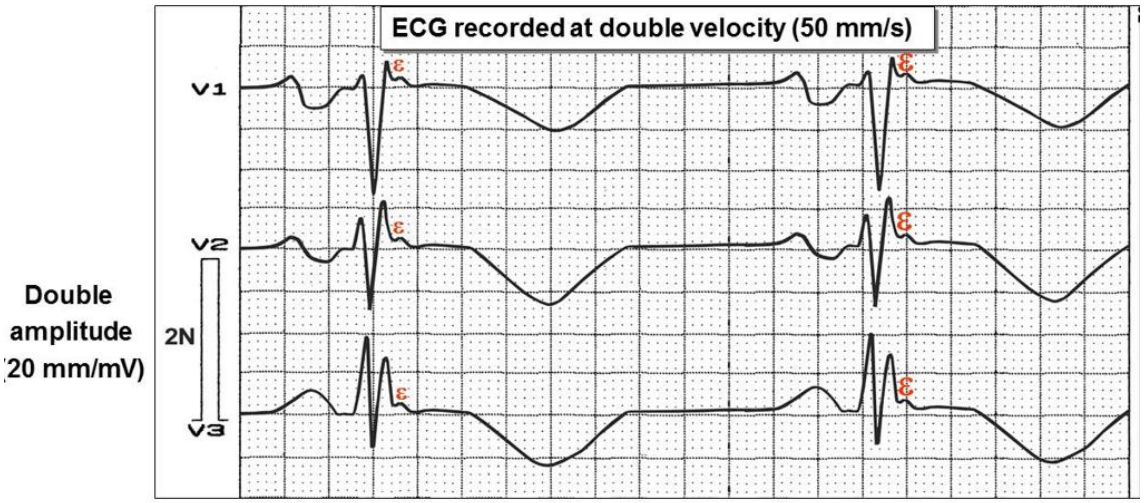


Figure. Epsilon wave (ε) characteristics in ACM.

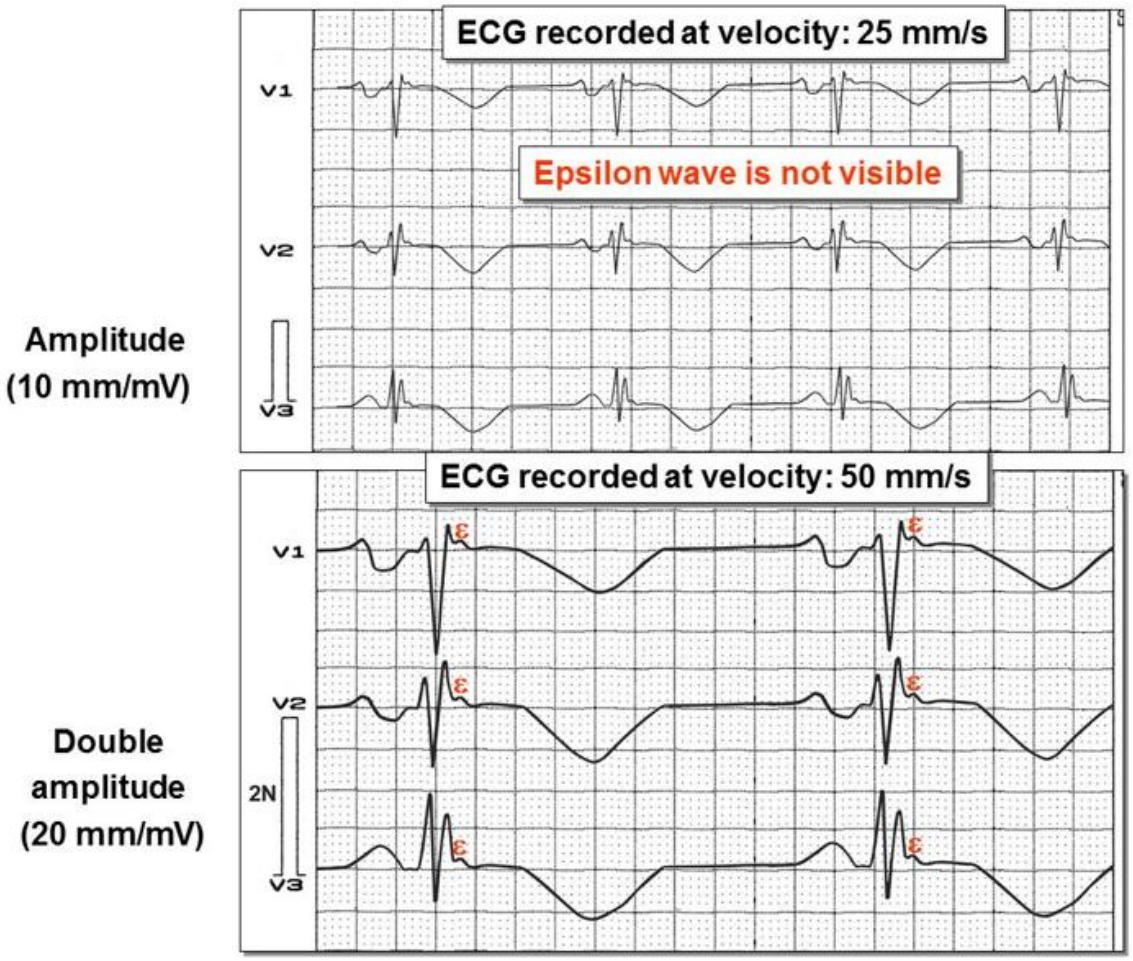


Figure. Epsilon wave (ε) characteristics in ACM.

Triangle of dysplasia in ACM

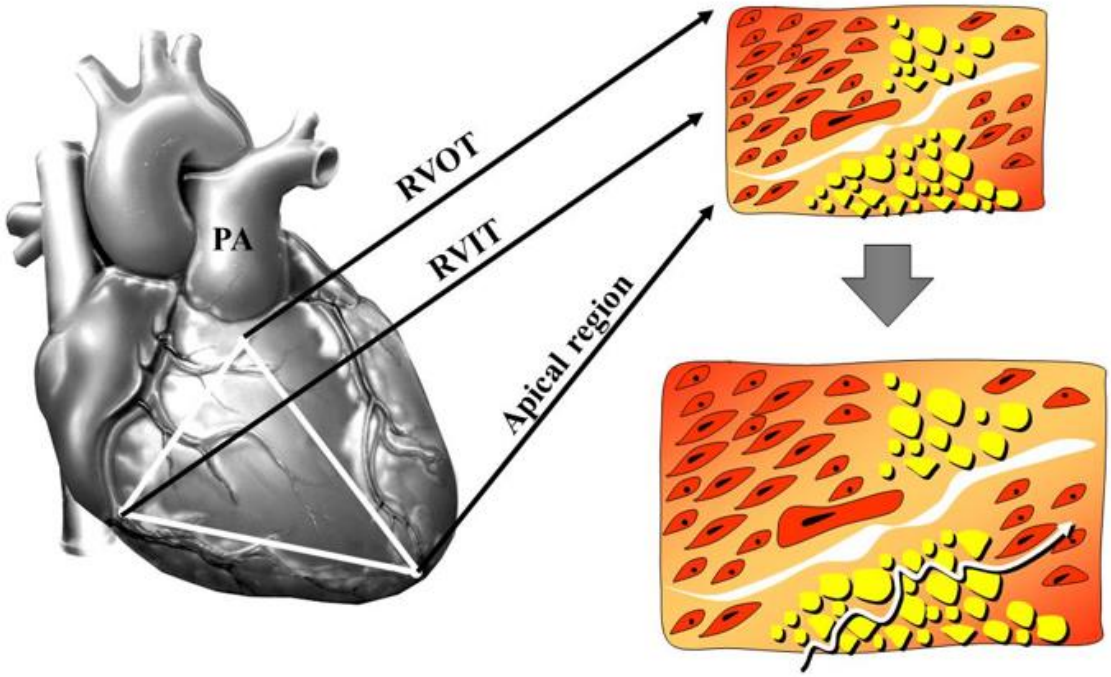


Figure. Triangle of dysplasia in ACM.

Outline of Epsilon wave in ACM

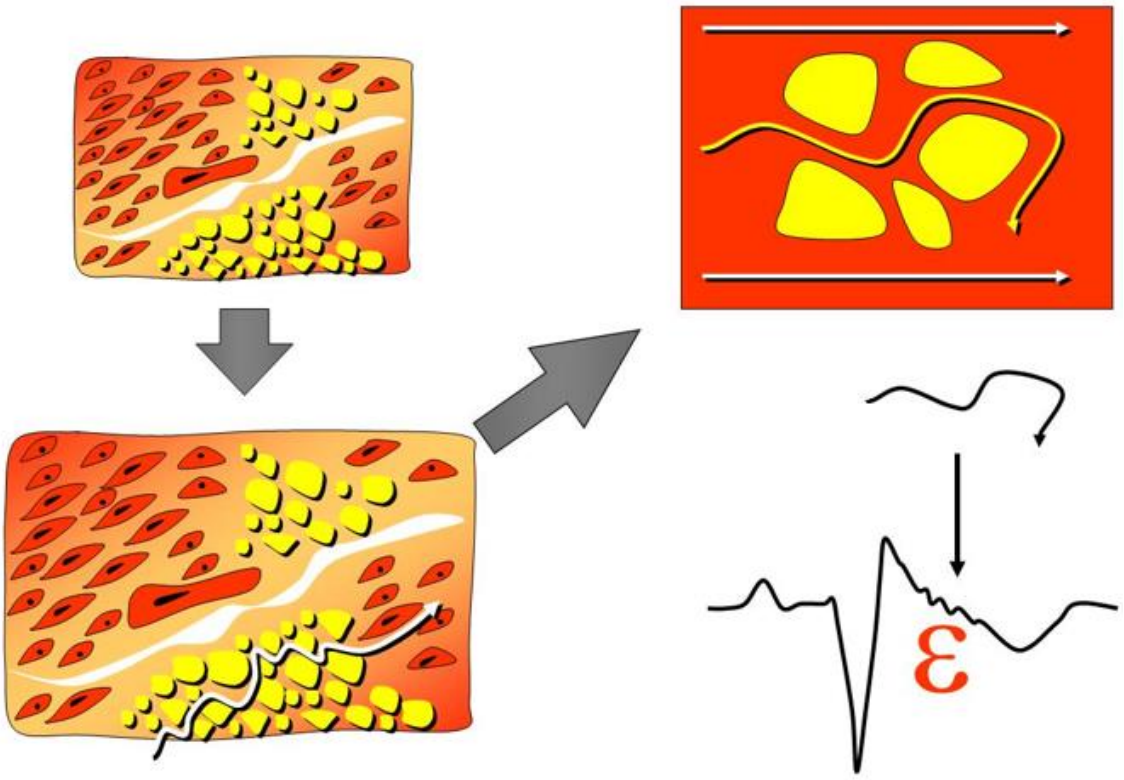


Figure. Outline of Epsilon wave in ACM.

Delta(δ), Epsilon (ε), and J waves location on ECG/VCG

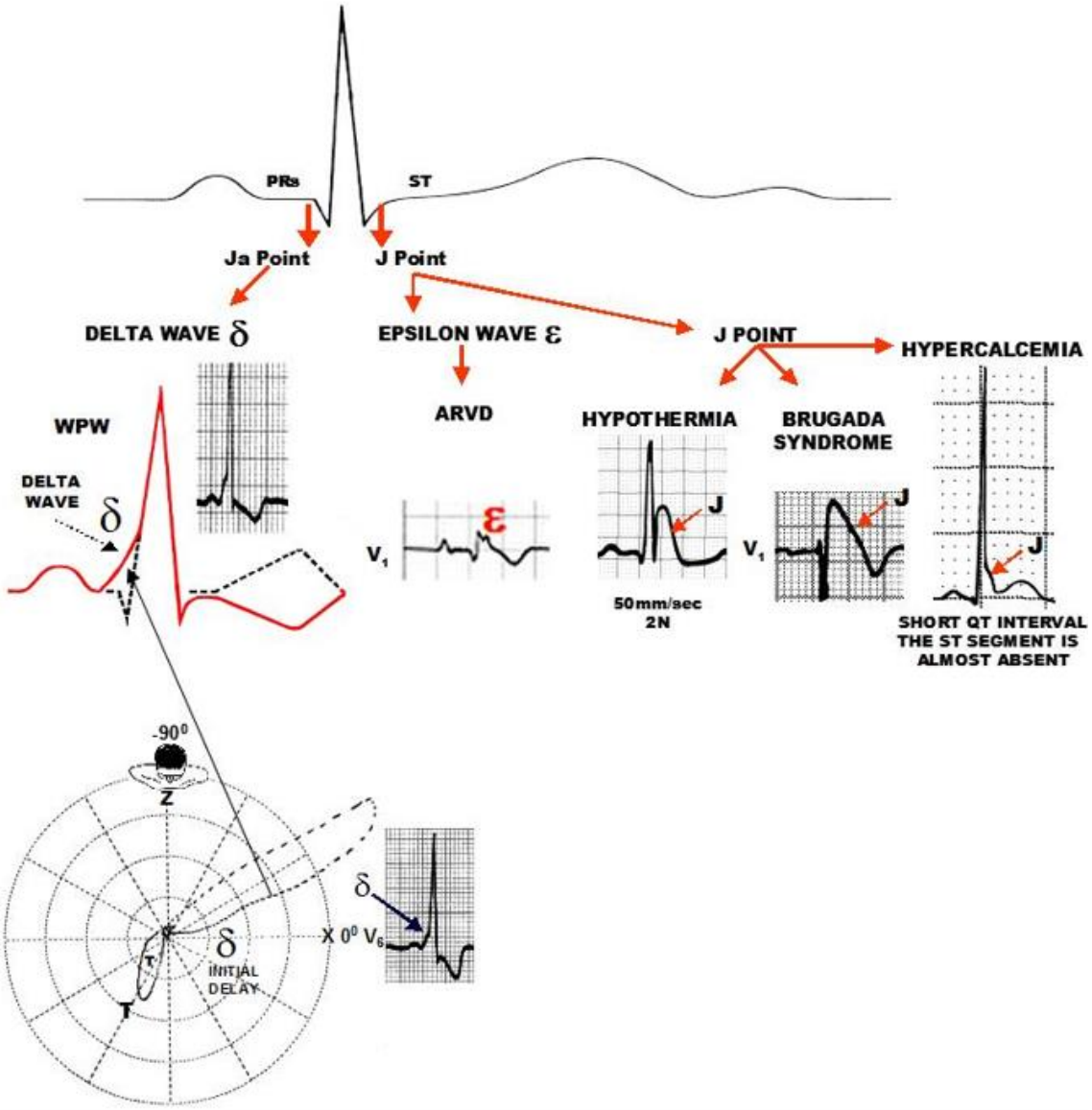


Figure . In WPW ventricular preexcitation, a wave located at the Ja point (end of PR segment and onset of QRS complex) is observed, called delta wave (δ). Following the Greek alphabet, the wave should be called Epsilon (ε), located near the J point (end of QRS complex and onset of ST segment).

Other electrocardiographic features in ACM

Complete RBBB (15%) or incomplete RBBB (RECD) (18%).[65]

Arrhythmias: Monomorphic SVT or NSVT VT with LBBB morphology .[173] [181] If SÂQRS of MVT with CLBBB morphology has inferior axis: it originates in RVOT. If SÂQRS of MVT with CLBBB morphology has superior axis: it originates in the RVIT.

Multiple morphologies of VT during the EPS and,

Frequent PVCs (>100º in 24h).[65]

QRST interval mapping reflects disparities in ventricular repolarization, which lead to vulnerability to arrhythmias. Integral mapping of QRST interval is considered an appropriate method to assess ventricular repolarization dispersion in patients with ACM.[65]

ACM associated with a high and significant incidence of inducibility for supraventricular tachyarrhythmias in the control population. Supraventricular tachyarrhythmias may precede induced VT.

TWI from V1 to V3 in ACM

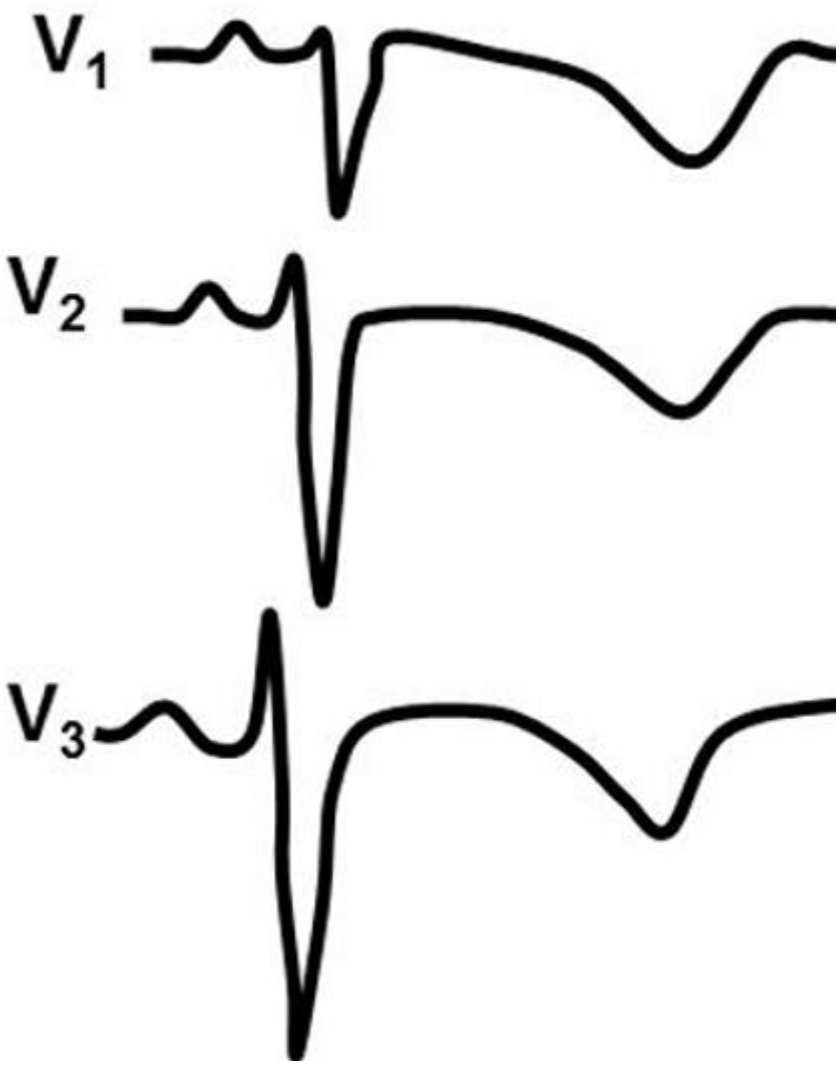


Figure X In the absence of CRBBB in patients >12 years old, negative T wave from V1 to V3 is a sign with great value for diagnosis. In normal, young patients, there is usually positive T polarity in V1; however, it may flatten and nearly always has a positive polarity in V2. In symptomatic patients with ACM, the ECG generally shows TWI in V1 and V2, which may reach up to V6. T wave from V1 to V3 in ACM.

Typical ECG of ACM with epsilon wave

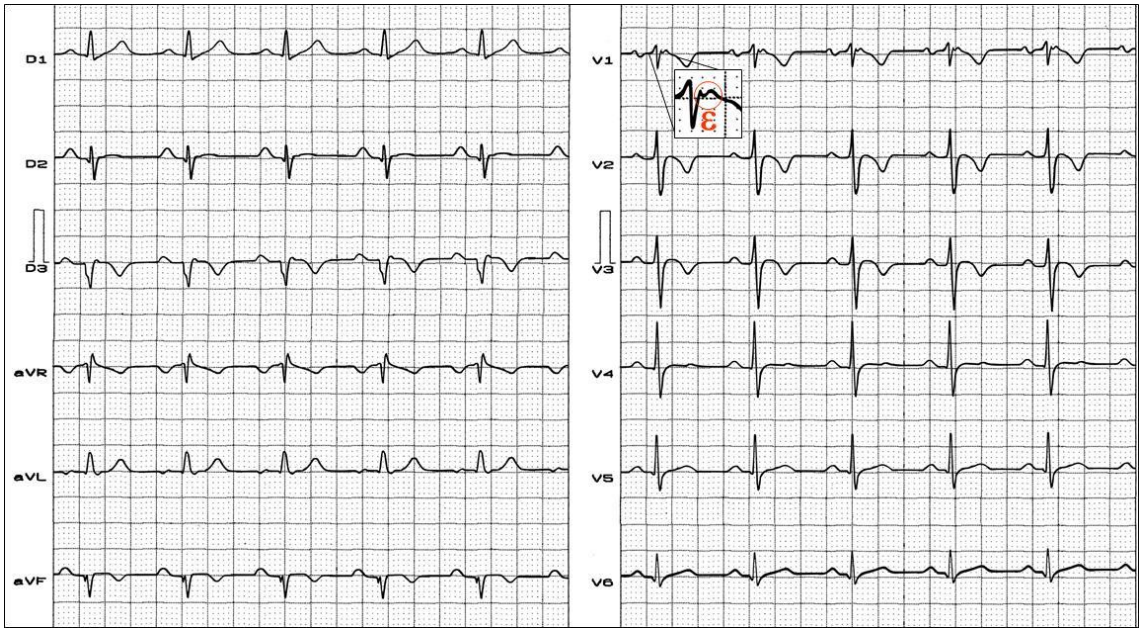
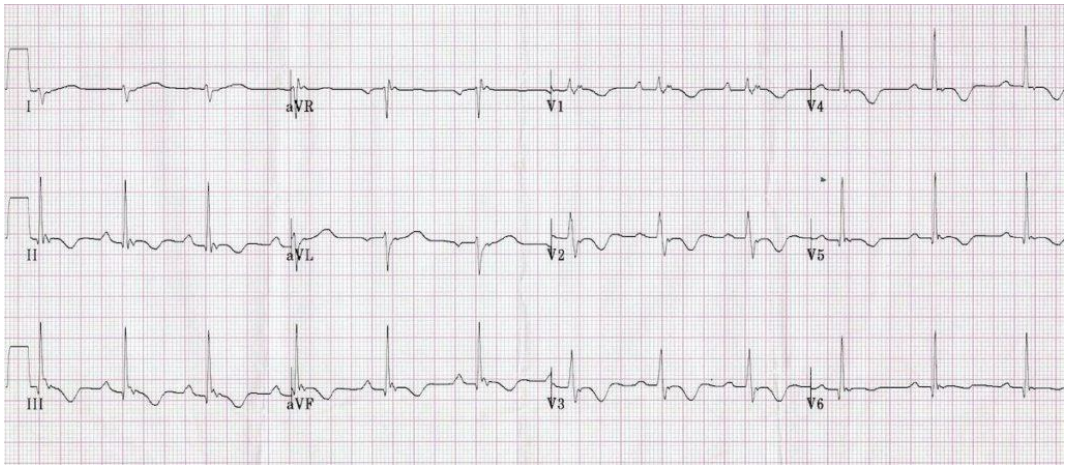


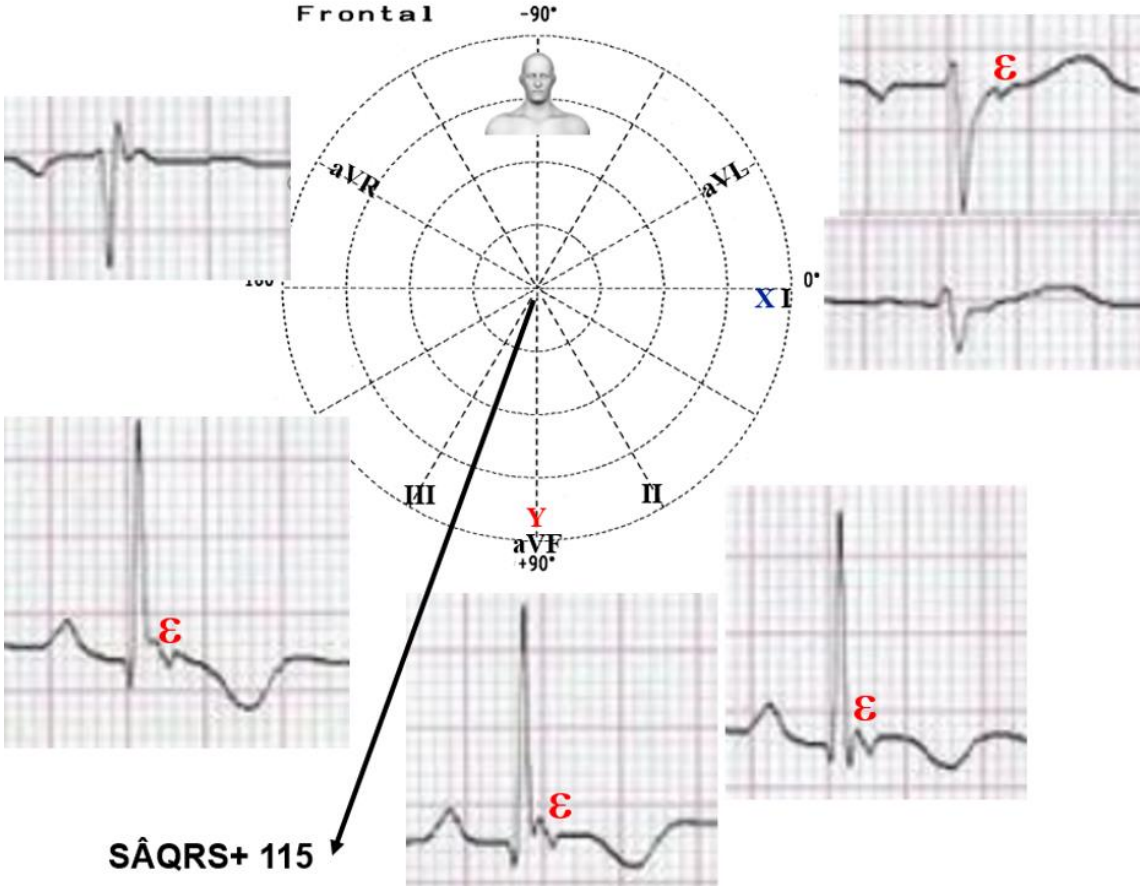
Figure. Clinical diagnosis: cardiac sarcoidosis. ECG diagnosis: SÂQRS -60º, negative TWI from V1 to V3, Epsilon wave (ε) in V1.

The two predominant causes of VT arising from the right ventricle are ACM and idiopathic VT arising from the RVOT. These arrhythmias can be adrenergically mediated and may be difficult to distinguish clinically. A minor criterion for the diagnosis of ACM is TWI in the right precordial leads during sinus rhythm. However, there have been reports of precordial TWI identified in patients with RVOT-VT. The purpose of this study was to determine whether patterns of precordial TWI could differentiate between the 2 groups. A multicenter registry of 229 patients with VT of RV origin was evaluated. After appropriate exclusions (n 29), 79 patients (58% men, mean age 40 ± 14 years) had ACM, and 121 patients (41% men, mean age 48 ± 14 years) had RVOT-VT. During sinus rhythm, 37 patients (47%) with ACM and 5 patients (4%) with RVOT-VT had TWI in leads V1 to V3. For the diagnosis of ACM, TWI in leads V1 to V3 had sensitivity of 47% and specificity of 96%. In conclusion, in patients with VT of right ventricular origin,

the presence of TWI in electrocardiographic leads V1 to V3 supports the diagnosis of ACM.[189]



Deviation of the electrical axis of the QRS to the right, dominant R wave in V1, generalized inversion of the T wave in inferior (II, III, aVF) and precordial (V1-6) leads, Subtle localized widening of the QRS complexes in V1-3, small wave following each QRS complex, best observed in V1 and lower leads: Epsilon wave.



Emerging Diagnostic tools for ACM. Source from Gandjbakhch et al.[49]

ECG	Imaging	Ventricular Arrhythmias	Tissue Pathology	Genetics
fQRS	Hypertrophic trabecular or hyper-reflective moderator band	Morphology of VAs: QRSd lead I >120 ms, QRS notching, transition V5	Voltage map guided biopsy	High-throughput sequencing and large panels of genes
V1=V2=V3 QRS duration >110 <ms	Decreased TAPSE and peak systolic RV annular velocity	VAs (PVC, NSVT, VT) originating from multiple RV sites		
V1 + V2 + V3/V4 + V5 + V6 widths ≥1.2 V1V2V3 QRS width ≥25 ms of V6 (parietal block)	Intra-myocardial fat infiltration in the RV wall. LGE of the RV wall;	VAs triggered by catecholaminergic stress Low sub-epicardial voltage areas in the RV; Isoproterenol test		

S-wave upstroke ≥55 ms fQRS TWI in inferior leads (LV extension) RBBB with R'/S ratio<1 in V1	Low peak systolic RV strain TTE speckle tracking, MRI feature tracking MDCT and 4D-cine CT	RV electroanatomic voltage map		

Abbreviations: TTE, transthoracic echocardiograph; RV, right ventricular; MRI, magnetic resonance imaging; MDCT, multi-dimensional computed tomography; CT, computed tomography; RBBB, right bundle branch block; LV, left ventricular; LGE, late gadolinium enhancement; VA, ventricular arrhythmia; TAPSE, tricuspid annular plane systolic excursion; PVC, premature ventricular contraction; NSVT, non-sustained ventricular tachycardia.

Differential diagnosis

The identification of LDAC and ALVC has made differential diagnosis more difficult because of the broader spectrum of phenocopies which requires a detailed study with appropriate evaluation of most prominent and discriminatory disease features. Conditions that enter into differential diagnosis of ACM include heart muscle diseases affecting the RV, the LV, or both. To confirm a conclusive

diagnosis of ACM, these differential possibilities need to be excluded by an accurate and targeted clinical evaluation. The currently etiologic classification of ACMs, whose common denominator is the distinctive phenotype characterized by a hypokinetic and non-dilated ventricle with a large amount of myocardial fibrosis underlying its propensity to generate ventricular arrhythmias is also addressed. The differential diagnosis for the ventricular tachycardia due to ACM include: Fatty infiltration of the RV free wall and/or presence of focal intra-myocardial fat, RVOT or idiopathic infundibular PVC/VT, athlete's heart, active myocarditis, sarcoidosis, Coronary artery disease and myocardial infarction, BrS, Uhl's anomaly, Ebstein's anomaly, interatrial septal defect, anomalous pulmonary venous return, tricuspid regurgitation, and inferior myocardial infarct with RV compromise.

1) Fatty infiltration of the RV free wall and/or presence of focal intra-myocardial fat

The differential diagnosis of ACM with Fatty infiltration of the RV free wall and/or presence of focal intra-myocardial fat is not easy.

See an erroneous interpretation using CMRI. figure x

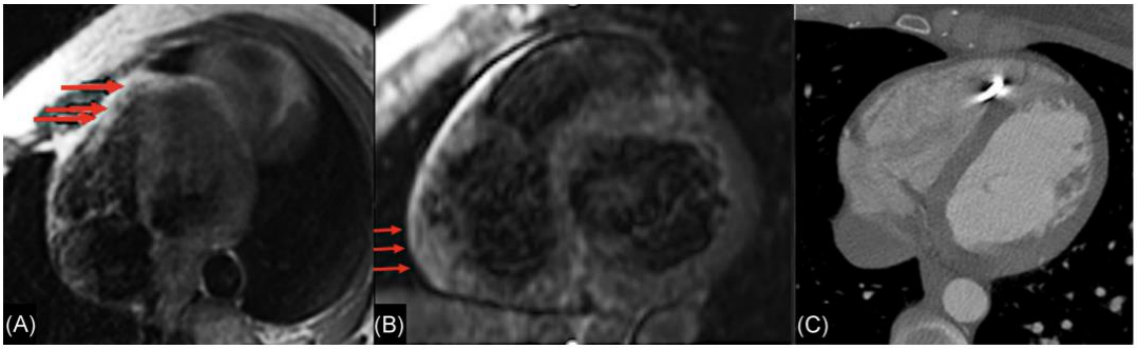


Figure x Representative CMRI (panel A, B) and CT (panel C) images of 24-year-old male misdiagnosed with ACM on CMRI. Fatty infiltration was reported to be

present in the mid to apical RV free wall at outside CMR read (red arrows in A, B). This was not confirmed on reread of the same CMR images. Indeed, CT did not show any evidence of RV fatty infiltration (panel C). ACM, arrhythmogenic cardiomyopathy; CMRI, cardiac magnetic resonance image; CT, computed tomography; RV, right ventricle

Physicians need to be aware of the updated diagnostic criteria. They also need to be mindful of the fact that CMRIs are frequently misinterpreted and that CMRI are only one part of the diagnostic criteria for ACM. The decision to implant an ICD should be made only after a firm diagnosis is established and this decision should be on the basis of whether a particular ACM patient's clinical features determine them to be a low, medium, or high risk of a future S-VT.[190, 191]

2) **ACM versus idiopathic RVOT-VT**

Differentiation between early-phase ACM and RVOT-VT can be challenging, and correct diagnosis is relevant. RVOT-VT is a form of monomorphic VT originating from the RVOT or occasionally from the tricuspid annulus. It is usually seen in patients without SHD. The two predominant causes of RVOT-VT are RVOT or idiopathic VT arising from the RVOT and ACM. The differential diagnosis between these 2 entities is critical, as their prognoses and therapeutic options differ. An incorrect diagnosis may be devastating. Both of these arrhythmias can be adrenergically mediated and may be difficult to distinguish clinically. RVOT is a clinical arrhythmic condition that is not typically associated with SHD as is seen in ACM. ECG and CMRI may be useful to distinguish these disorders.

The microvolt T-wave alternans (TWA or MTWA) is widely used to predict lethal ventricular arrhythmias in various diseases. However, the clinical significance of

TWA in patients with VT originating from the RV has been unknown. TWA refers to beat-to-beat fluctuations of T-wave amplitude and morphology, and is associated clinically with impending ventricular arrhythmias and increased risk of SCD. TWA analysis can be done as part of an exercise stress test or during a Holter monitoring recording. Within candidates for ICD therapy, a negative TWA test may be useful in identifying low-risk patients who are unlikely to benefit from ICD placement. However, currently there is not enough evidence to support the use of TWA in clinical practice to guide therapy.[192]

Yalin et al aim to investigate the possible role of TWA to discriminate ACM from idiopathic RVOT-VT. They enrolled 38 patients (23 males, 43 ± 16 years) with VT originating from the RV. TWA was measured during exercise testing using a modified moving average method. TWA results were compared among patients with ACM and RVOT-VT. Twenty-five patients (16 males, 42 ± 16 years) met the Task Force 2010 criteria for the diagnosis of ACM, and 13 patients (7 males, 45 ± 14 years) had idiopathic RVOT-VT. Twenty patients with ACM had positive TWA test, whereas only 1 patient with RVOT-VT had (80% versus 8%, $P < 0.001$). In patients with VT of RV origin, positive TWA test supports the diagnosis of ACM.[193] Absence of significant TWA in a patient with cardiac disease with CHF, low ejection fraction or a recent MI is associated with a low risk of SCD. The table x shows the main differences between ACM with Idiopathic RVOT-VT

2)Differential diagnosis between ACM and Idiopathic RVOT-VT

I) Prevalence

- **ACM:** The estimated prevalence of ACM in the general population ranges from 1 in 1,000 to 1 in 5,000.[194] Peters refers 1:1,000 to 1:1,250[33] or 1:2,000–1:5,000.
- **Idiopathic RVOT-VT/PVC:** There was a high prevalence of J-waves in the idiopathic RVOT-VT/PVC patients referred for RFCA. Although patients with idiopathic RVOT-VT/PVC associated with J-waves might have a more enhanced arrhythmogenicity than those without J-waves, the significance of those J-waves was limited in terms of the prognosis and VF.[195]

II) Presence of gene mutation and inheritance pattern

- **ACM:** gene mutation ≈ 80% positive predominantly in desmosomes with inheritance pattern autosomal dominant (AD), autosomal recessive (AR), *Compound Heterozygosity or Digenic Mutations.* Gene mutations have been found in about 60% of people with ACM. Mutations in a desmosomal gene PKP2(**plakophilin-2**) appear to be most common. Of patients with plakophilin-2 genetic variants, 25 of 38 (65.7%) were found to have a second plakophilin-2 abnormality or a second abnormal desmosomal gene.[130] In people without an identified mutation, the cause of the disorder is unknown. Researchers are looking for additional genetic factors that play a role in causing ACM. ACM confirmed in a first-degree relative who meets current TFC; ACM confirmed pathologically at autopsy or surgery in a first-degree relative Identification of a pathogenic mutation categorized as associated or probably associated with ACM in the patient

- **Idiopathic RVOT-VT/PVC:** No. They are the most common subtype of idiopathic ventricular arrhythmias. Research conducted under the leadership of Weill Cornell Cardiology Professor Bruce Lerman since the 1980s has suggested that RVOT is caused by a mutation in the gene for a protein called Gsα, and indeed such a mutation has been discovered in cardiac cells in Dr. Lerman's laboratory.[196]

III) Sex M/F ratio

- **ACM:** M/F 3:1[197] Sex-based differences in the incidence are conflicting. Italian studies report that it is more common in males with an approximate ratio of 3:1,[37] on the other hand the United States and the Dutch ACM cohorts report similar incidence between males and females.[3, 38] European studies (predominantly from the Netherlands) and the United States show that AMC is 1.2–3 times more common in males.[3, 37, 38, 198, 199] However, the male predominance is not observed in USA Registry (89% of males vs. 84% of females).
- **Idiopathic RVOT-VT/PVC:** M/F 24%/76% male/female ratio 0.49.[200]

IV) Age of presentation

- **ACM:** Early-phase ACM patients are younger than the RVOT-VT patients, a result of the early detection of ACM mutation positive by family screening.
- **Idiopathic RVOT-VT/PVC:** Typically seen between 20 and 50 years of age.

V) Geographic distribution

- **ACM:** Worldwide (Italy/Padua. Naxos island AR variant. The non desmosomal gene TMEM43-endemic to Newfoundland, Canada. To date, all familial cases reported worldwide share a common ancestral haplotype.[75]
- **Idiopathic RVOT-VT:** Worldwide.

VI) Main clinical manifestations

- **ACM:** Asymptomatic (6.2%), Palpitations (67%), Exertional pre-syncope, syncope (32%), atypical chest pain (27%) or SCD. Syncope: more prevalent. Not unexpectedly, SCD/CA: more prevalent.
- **Idiopathic RVOT-VT/PVC:** Asymptomatic (26,6%). palpitation (30%), presyncope (43,4%) lightheadedness often provoked by sympathetic stimulation during exercise or emotional upset. Syncope: occasionally observed. Lesser prevalent. Not unexpectedly, SCD/CA: Rare. Triggered by stress or exercises, gestation, extreme consumption of alcohol, coffee or tobacco

VII) ECG manifestations

- **ACM: Depolarization features:** QRS duration in right precordial leads ≥105 ms registered in≈ 80% of case; TAD of QRS ≥55 ms: Present in ≈30% of cases, specificity of 100%. Excellent accuracy.; *Epsilon wave:* Present in 30% of cases with conventional 12-leads ECG, in the right precordial leads (Mayor criteria?). Its identification and interpretation are influenced by ECG filtering and sampling rate, with large interobserver variability.[147] Consequently, currently

Padua researches, consider epsilon waves in right precordial leads a minor ECG criterion.

Repolarization features: JT interval duration in right versus left precordial leads ≥1.15: Yes: parietal block. High specificity = 97%. TWI from V1 to V3 during sinus rhythm in absence of IRBBB or CRBBB is registered in 15% of cases: specificity very high and moderate sensitivity. TWI typically remain inverted during exercise.[201]

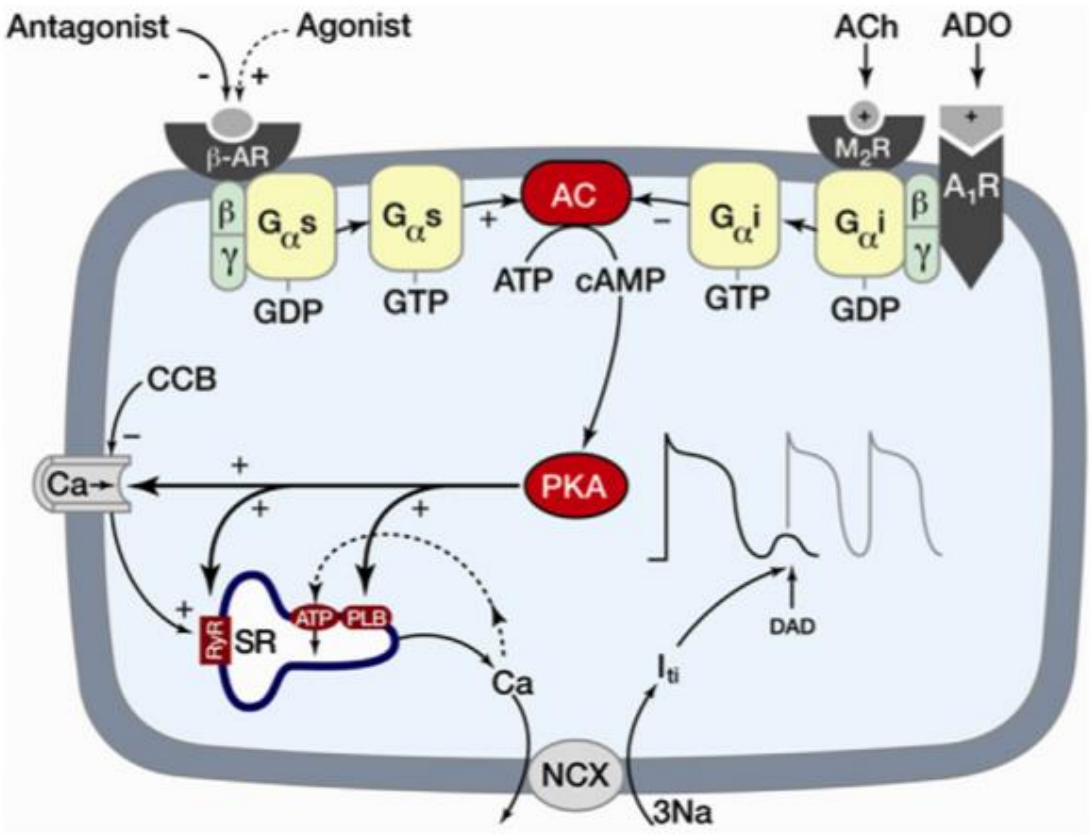
- **Idiopathic RVOT-VT/PVC: Depolarization features:** QRS duration in right precordial leads ≥105 ms absent or rare. TAD of QRS ≥55 ms: Absent.; Epsilon wave**:** Absent; **Repolarization features:** JT interval duration in right versus left precordial leads ≥1.15: Absent.; TWI from V1 to V3 during sinus rhythm: rare: 1% of cases. TWI typically normalize during exercise among athletes.[145]

VIII) Ventricular arrhythmias

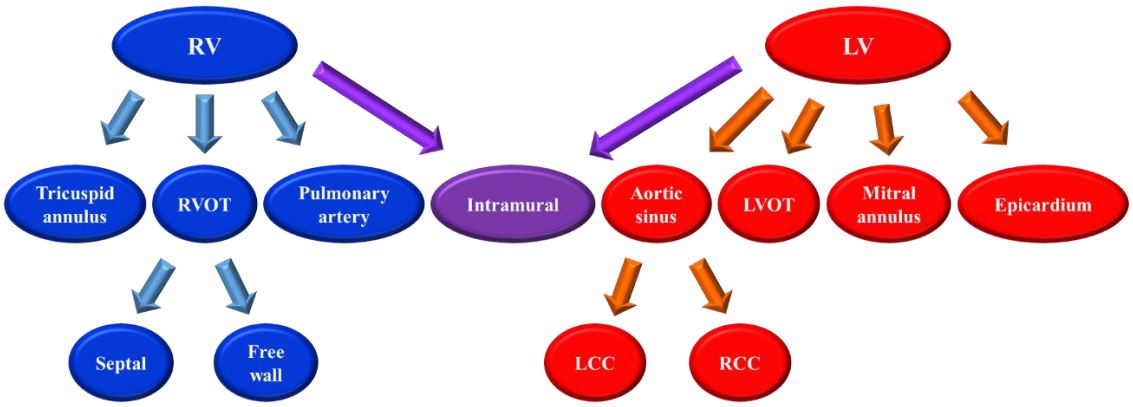
- **ACM:** PVCs frequency: Relatively low number, less frequent PVCs and NSVT in early-phase; PVCs of RVOT: In early-phase, ACM frequent origin of PVC mainly the **septal** part of the RVOT (98%).[202] Polymorphic VT and VF: More common and generally familial; **Morphology of monomorphic VT**: NSVT or SVT of LBBB morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL). It is considered a major criterion; Mechanism of VT: Reentry originate from fibro-fatty replacement of myocardium forming the substrate for VT. In early

phase, other mechanisms may be involved including disruptive electrical conduction in addition to early fibrosis.[203] Event triggers: During exercise. ACM accounts for up to 20% of cases of SCD in young athletes.[204, 205]

- **Idiopathic RVOT-VT/PVC:** PVCs frequency: More frequent. PVCs predominant, site of origin of PVC in the **lateral** free wall of RVOT.[206] Polymorphic VT and VF: Rare. VTs are monomorphic and generally not familial. **Morphology of monomorphic VT**: NSVT of LBBB morphology with inferior axis (right or left) with tall R waves in leads II, III, and aVF. The arrhythmia may present occasionally with SVT, NSVT or PVCs, often provoked by exercise or emotional upset.; **Mechanism:** adenosine-sensitive, cyclic AMP mediated, triggered activity.[207, 208] Figures



Mechanism of outflow tract tachycardia. Signal transduction schema for initiation and termination of cAMP mediated triggered activity. AC ¼ adenylyl cyclase; ACh ¼ acetylcholine; ADO ¼ adenosine; A1R ¼ A1-adenosine receptor; β-AR ¼ β-adrenergic receptor; CCB ¼ calcium channel blocker; DAD ¼ delayed afterdepolarization; Iti—transient inward current; M2R ¼ muscarinic receptor; NCX ¼ Naþ/Ca2þ exchanger; PLB ¼ phospholamban; PKA ¼ protein kinase A; RyR ¼ Ryanodine receptor; SR ¼ sarcoplasmic reticulum. (Reproduced with permission from Lerman [11].)



Classification of outflow tract tachycardia. LCC ¼ left coronary cusp; LV ¼ left ventricle; LVOT ¼ left ventricular outflow tract; RCC ¼ right coronary cusp; RV ¼ right ventricle; RVOT ¼ right ventricular outflow tract.

According to the QRS configuration during episode of IM-VT four groups were distinguished by Mont et al.[209]

1) Group I: RBBB morphology and SÂQRS superior in the frontal plane: This group had dizziness during VT less frequently, but they needed cardioversion to terminate their arrhythmias more often. They experienced tachycardia during exercise less often, and tachycardia was not initiated during exercise testing. They had fewer PVCs according to the Holter recording. During the EPS, VT was

induced and terminated by pacing more often in this group. Reentry seems to be the most likely arrhythmia mechanism in this group.

2) Group II: RBBB morphology and intermediate SÂQRS on frontal plane;

3) Group III: LBBB morphology and left axis deviation;

4) Group IV: LBBB morphology wit right axis deviation or intermediate;

IX) TTE

- **ACM:** Increased RV diameters, Additionally, RV function is decreased, and RV mechanical dispersion is pronounced. LV function is reduced. LVEF and Left ventricular global longitudinal strain (LVGLS), and LV mechanical dispersion is more pronounced.
- **Idiopathic RVOT-VT:** All RV diameters are within normal range in the RVOT-VT patients. RV function is in the lower normal range.

X) 3-dimensional Electro Anatomical Voltage Mapping (EVM) Right ventricular EVM identify low-voltage regions ("electroanatomical scar"), which in patients with ACM correspond to areas of fibrofatty myocardial replacement.

- **ACM:** An early/minor form of ACM may mimic idiopathic RVOT-VT. EVM is able to identify Idiopathic RVOT-VT due to concealed ACM by detecting RVOT electroanatomical scars that correlate with fibrofatty myocardial replacement at EMB and predispose to SCD.[210]
- **Idiopathic RVOT-VT/PVC:** Electroanatomical voltage mapping was normal in 74%, with electrogram voltage >1.5 mV throughout the RV.[210]

XI) Cardiac Magnetic Resonance Image (CMRI)

- **ACM:** Visualization of fibro-fatty infiltration on T1-weighted images.
- **RVOT-VT/PVC:** Is normal presence of fat in the AV groove and anteroapical RV epicardium. Artifacts due to motion, arrhythmia, and surface coil proximity can reduce specificity.[211] It is particularly important to exclude mild forms of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Patients with a family history of SCD and apparent RVOT-VT should be particularly thoroughly with a CMRI.

XII) RV ejection fraction:

- **ACM:** Limited value
- **RVOT-VT/PVC:** RV highly effective

XIII) Endomyocardial biopsy (EMB)

- **ACM:** Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
- **Idiopathic RVOT-VT/PVC:** Idiopathic VT is defined as VT that occurs in patients without SHD, metabolic abnormalities, or the LQTS. Usually negative: without structural heart disease. Studies with EMB contradict this concept, having shown abnormalities in more than 65% of cases, which increases to more than 80% when the material is product of an autopsy. Thus, the following were described:[212] Indicatives of SHD: Hamartoma of Purkinje fibers was

described.[213] Mild form of ACM; microangiopathy associated to subendocardial fibrosis, sub-clinical myocarditis, focal cardiomyopathy, atherosclerotic ischemic cardiomyopathy, non-atherosclerotic ischemic cardiomyopathy, hypertrophic cardiomyopathy and mitral valve prolapse.

XIV) Prognosis

- **ACM:** Tendency to ventricular arrhythmias, biventricular dysfunction, cardiac syncope, SCD and therefore a far from a benign condition.[214]
- **Idiopathic RVOT-VT:** Usually benign, but occasionally can induce LV dysfunction, and, very rarely, VF or polymorphic VT. It is supposed to be a relatively benign condition.[215] Until relatively recently, outflow tract (OFT) arrhythmias OFT PVCs were considered benign. However, this notion has been invalidated by reports over the last 15 years, showing that a small cohort of these patients can present with polymorphic VT/VF.[215-218] This condition may be mistaken for ACM or idiopathic VF. Since malignant OFT arrhythmias are amenable to definitive cure with RFCA, it is imperative to recognize this variant. The key is to show that a patient's isolated and putatively benign PVCs share the same morphology as the PVCs that trigger the malignant arrhythmia, indicating an identical origin for both phenomena. Successfully targeting the triggering PVC is sufficient to effect cure of polymorphic VT or VF; however, it is advisable to also implant an internal CDI should the PVC suddenly reemerge. In general,

malignant OFT triggering PVCs have short coupled, usually landing on the preceding T wave sinus beat. The coupling interval is often but not always shorter than that associated with benign OFT PVCs (and is longer than that associated with idiopathic VF).[215, 219] Igarashi et al. suggested that a prematurity index (coupling interval PVC/sinus cycle length) distinguishes between malignant from benign PVCs. A prematurity index r0.73 has a sensitivity of 91% and a specificity of 44% for identifying malignant PVCs.[220] However, Kim et al. not confirmed this finding and have instead proposed that the coupling interval of the second PVC during runs of NSVT better differentiates between malignant and benign forms of OFT PVCs (313 ms vs. 385 ms, respectively).[221] At present, it is reasonable to conclude that the best metric for identifying malignant PVCs is unsettled and that no single parameter consistently distinguishes between malignant and benign OFT PVCs.

XV) Management

- **ACM:** Restriction from high endurance and competitive sports (Exercise has a disproportionate role in the pathogenesis of ACM in patients without desmosomal mutations.[222, 223]

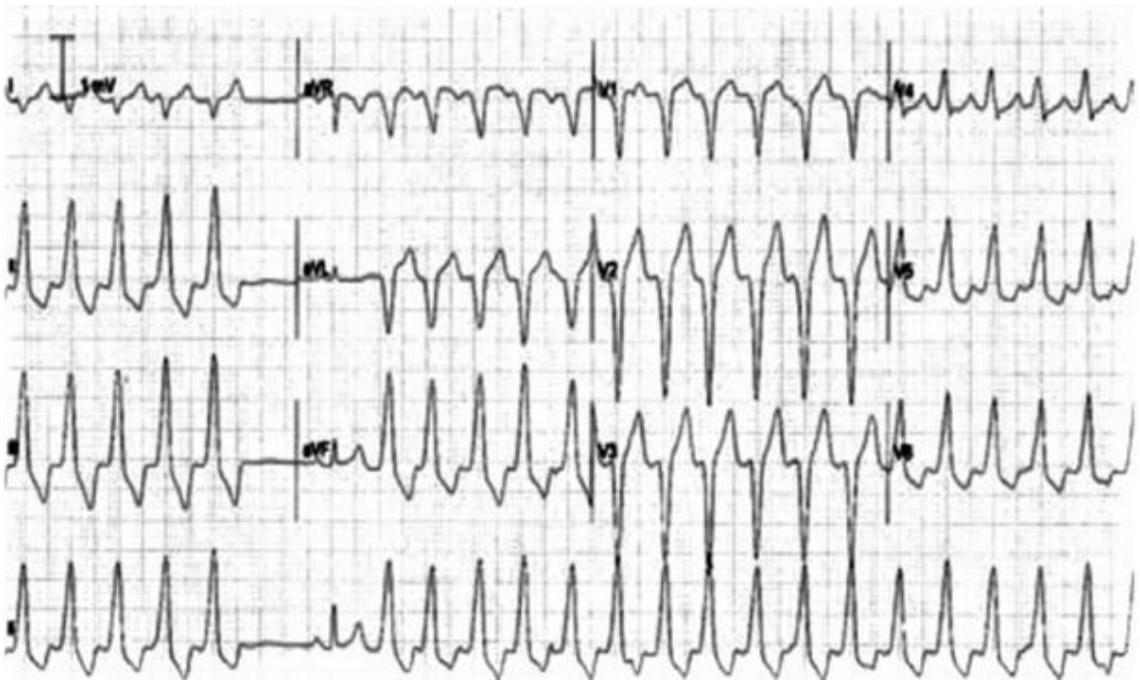
  B- blockers (BBs): CHF treatment,

  ICDs: In cases of S-VT, ventricular flutter (as defined as a CL ≤ 240 msec), or VF

  Hemodynamically stable VT (polemic): Combined endocardial/epicardial RFCA of choice for recurrent MACE in ACM. patients with ACM who experience a SVT arrhythmia,

regardless of hemodynamic stability, have a sufficiently high risk of SCD to warrant placement of an ICD.[224]

- **Idiopathic RVOT-VT:** Treatment options include medical therapy vs. RFCA of RVOT. Acute termination of RVOT VT can be achieved by vagal maneuver or adenosine (6 mg up to 24 mg). Intravenous verapamil (10 mg given over 1 min.) is an alternative if the patient has adequate blood pressure. RFCA of RVOT has acute success rates > 80% (range, 85% to 100%). Recurrence up to 5% of cases with the mean recurrence rate of 7%.



12-lead ECG of a 36-year-old pregnant woman admitted with a 4-week history of increasingly intrusive palpitations associated with presyncope. Bursts of broad complex VT are seen with a LBBB morphology, inferior axis (right) with tall R waves in leads II, III, and aVF and precordial transition at V4 consistent with origin from the RVOT.[153] With permission.

A scoring system was proposed by Hoffmayer et al[225] to distinguish between ACM from idiopathic VT provides the following values:

- 3 points for sinus rhythm anterior TWI in leads V1–V3 and during ventricular arrhythmia;
- 2 points for QRS duration in lead I ≥120 ms;
- 2 points for QRS notching;
- 1 point for precordial transitional lead V5 or later.

A score of 5 or greater was able to correctly distinguish ACM from idiopathic VT 93% of the time, with a sensitivity of 84%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 91%.

3) Highly trained athletes Athlete's heart adaptations versus ACM

Regular intensive physical activity is associated with no pathological changes in cardiac morphology referred to as “athlete’s heart”. Nonetheless, in the athletic population, the presence of RV and atrial adaptations, in particular dilatation, is described and has to be considered in the differential diagnosis with ACM which is an important cause of SCD in young athletes. Bauce et al data suggest that athlete’s heart can be differentiated from ACM through an accurate clinical and instrumental non-invasive evaluation protocol including ECG, SAECG and TTE. ECG findings suggestive of ACM include the presence of a negative TWI beyond V1 in the precordial leads, incomplete RBBB and low QRS voltage. Both athletes and ACM patients demonstrate RVH compared with controls; however, RV cavity size is not significantly larger in ACM patients than in athletes. On the contrary, ACM is significantly larger in ACM subjects compared with athletes. Furthermore,

all ACM patients show localized RV kinetic alterations, an abnormality not detected in athletes and controls.[201]

Physical exercise has been identified as a strong determinant of phenotypic expression of the ACM, arrhythmia risk, and disease progression. Current guidelines advise that individuals with ACM should not participate in competitive or frequent high-intensity endurance exercise. Exercise-induced electrical and morphological para-physiological remodelling (the so-called 'athlete's heart') may mimic several of the classic features of ACM. Therefore, the current International Task Force Criteria for disease diagnosis may not perform as well in athletes. Clear adjudication between the two conditions is often a real challenge, with false positives, that may lead to unnecessary treatments, and false negatives, which may leave patients unprotected, both of which are equally inacceptable.

Similitudes and divergences between ACM and Athlete heart. Table x and Figure x

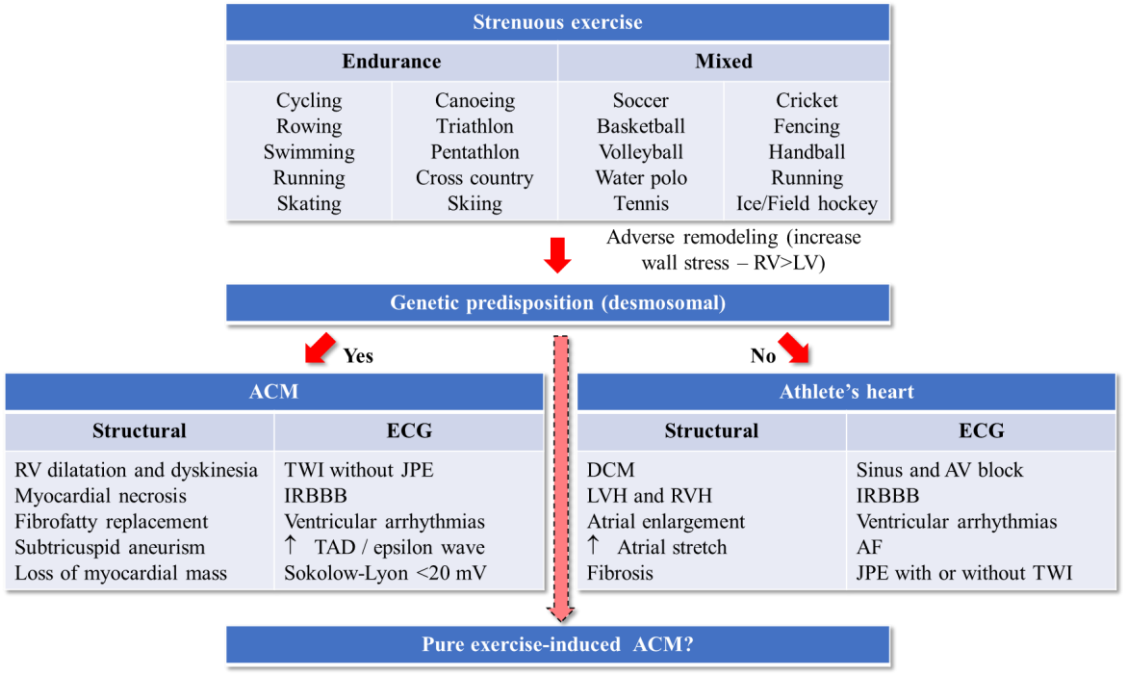
ACM	Athlete heart
Structural/image: RV dilatation akinesia and dyskinesia (wall motion abnormalities), myocardial necrosis, fibro-fatty replacement, loss of myocardial mass (LGE), macroscopically detectable changes, both at CMRI and/or EMB.[226]	Structural/image: dilated cardiomyopathy, atrial enlargement, atrial stretch augmentation, LVH, RVH without akinesia, fibrosis, no fibro-fatty replacement.
ECG alterations in 80%:[227] no J-point elevation, extensive TWI, IRBBB,	ECG alterations: sinus and AV block, IRBBB, Ventricular arrhythmias, AF, J-

CRBBB (RBBB is not frequent in early stages, but its overall reported prevalence is not low and may increase over time,[228] TAD, epsilon wave, positive Sokolow-Lyon criteria.	point elevation followed by TWI, positive Sokolow-Lyon criteria.
Exercise stress test BNP and pro-BNP correlate with the extension of LV involvement[229]	**Exercise stress test** **I**ncreases in levels of circulating cardiac biomarkers: troponin T, D-dimer, B-type natriuretic peptide (BNP), and N-terminal pro-BNP after physical exercise
Transthoracic Echo (TTE) TTE often is the first-line imaging modality in a patient with suspected ACM because of its widespread availability and low cost. TTE provides structural and functional information on all cardiac chambers, although visualization of the RV requires special emphasis and expertise. In addition, in patients with an ICD, TTE may be used for serial evaluation to evaluate disease progression. CMR has high spatial resolution and a theoretically unlimited field of view,	Transthoracic Echo (TTE) Increased RV mass and cavity size, alongside with an increase in wall thickness and reduction in global systolic function.[231] Up to 81% of athletes show a round-shaped apex, and both prominent RV trabeculations and hyperreflective moderator bands have been reported in healthy athletes.[232] Due to this remodeling, isolated RV measurements at echocardiography do not seem to be useful in differentiating physiologic from pathologic RV dilation. D'Ascenzi

thereby allowing for detailed visualization of RV wall motion abnormalities. In addition, the 3-dimensional (3D) depiction of anatomy by CMR enables accurate measurement of RV volumes and function.[230]	et al[232] reported that 41% and 16% of healthy Olympic athletes in their case series presented an RVH within range of minor and major criteria for ACM, respectively. These numbers increased to 50% and 25%, respectively, in a sub-analysis of the same cohort considering endurance athletes only. Oxborough et al. reported in a 102 athlete cohort, with 28% of endurance athletes presenting RVOT diameters greater than the ACM major criteria cut-off values.[233] Zaidi et al. demonstrated apical RV motion abnormalities at TTE and RV fractional area change between 31% and 40%, both contained in the ITFC, to be poor discriminators for ACM among athletes.[234]
Family history Unexplained SCD in family	Family history First in family proband
Irreversible Stop competitive sport eligibility	Reversible. competitive sport eligibility[235]
Necessary screening family members using a genetic panel comprising of at	Negative genetic testing cannot rule out the disease.

least all desmosomal genes: DSP (125647), PKP2 (602861), DSC2 (125645), or DSG2 (125671)[236]	
EMB Fibro-fatty replacement is the hallmark of AMC. Low sensitivity and specificity. Risk complications,	EMB Indicate in competitive athletes with ventricular arrhythmias (VAs) and an apparently normal hearts. Three-dimensional electroanatomic mapping (EAM) has been demonstrated to reliably identify low-voltage areas that correspond to different cardiomyopathic substrates. This resource may help diagnose concealed myocardial diseases in competitive athletes presenting with recent-onset VAs and an apparently normal heart. Further studies are warranted to assess the prognostic implications of such subtle myocardial abnormalities.[237]
Voltage map guided EMBs: promising results.[168, 237-239]	As a 'rule-out' test have been published, with overall good results.[237, 240]

Figure x illustrate similitudes and divergences between ACM and Athlete heart.



The modifications induced by strenuous exercise lead to the development of structural and electrical ACM phenotype (Red Box) upon the presence of an underlying genetic predisposition, while inducing the clinical characteristics of the athlete's heart in the general population (Blue Box). The possibility of developing a pure exercise-induced ACM (Purple Box) upon massive exposure to strenuous exercise in the absence of genetic predisposition has been postulated but its existence is still debated (Dashed line). AV, atrio-ventricular; JPE, J-point elevation; LV, left ventricle; LVH, left ventricular hypertrophy; RBBB, right bundle branch block; RV, right ventricle; RVH, right ventricular hypertrophy; TAD, terminal activation duration; TWI.[241]

	Athlete's heart adaptations (highly trained athletes)	**ACM**
QRS duration	Normal	Prolonged

Low QRS voltages	Very rare	Suggestive
Conduction delay	High incidence	Infrequent
TWI beyond V2	Rare	Suggestive
Normal ECG	97%	38%
QRS voltages	Higher: myocardial hypertrophy	Normal or lower: progressive myocardial atrophy
Ventricular arrhythmias	5%	70%
The ratio between LV and RV end-diastolic volumes	Similar	Significantly smaller
RVOT diameter	Smaller	Significantly larger
RV kinetic alterations,	No	Yes: Localized RV kinetic alterations
RV cavity size	Is not significantly smaller	Is not significantly larger
Moderator band	Normal	Thickened and/or high reflective

Diagram for distinguishing between subclinical dilated cardiomyopathy (DCM)

from athletic heart syndrome

Athletes´s heart		Subclinical DMC
(-)	**Family history of SCD or DMC**	**(+)**
(-)	**Family screening for DMC**	**(+)**
(-)	**Genetic testing**	**(+)**
(-)	**Abnormal ECG**	(±)
(-)	**Complex/frequent ventricular arrhythmias**	**(+)**
(±)	**Myocardial fibrosis**	**(+)**
>80%	**Percent of predictive peak VO_2#**	**<80%**
<17%	**Global Longitudinal Strain**	**>17%**
(-)	**Elevated BNP/ -proBNP levels**	**(+)**
(-)	**Elevated Troponin**	**(+)**
(+)	**EF increase by >11% by exercise***	(-)

Diagram for distinguishing between subclinical DCM and athletic heart syndrome. BNP, brain natriuretic peptide; DCM, dilated cardiomyopathy; ECG, electrocardiogram; EF, ejection fraction; NT-proBNP, N-terminal pro hormone BNP; SCD, sudden cardiac death; VO_2, oxygen consumption. # For a pathogenic or likely pathogenic variant in a gene associated with dilated cardiomyopathy, * excluding Troponin rise after strenuous exercise.[242]

4) Myocarditis mimicking ACM versus ACM

Right ventricular myocarditis frequently mimics ACM. Three-dimensional electroanatomic mapping-guided endomyocardial biopsy is a safe and effective tool in differential diagnosis and in the selection of the most appropriate therapeutic strategy.[243, 244]

Table X lists three-tier classification scheme for the diagnosis of myocarditis.[245]

Classification	Criteria
Possible subclinical acute myocarditis	In the clinical context of possible of myocardial injury without cardiovascular symptoms but with at least one of the following: 1. Biomarkers of cardiac injury raised; 2. ECG findings suggestive of cardiac injury; 3. Abnormal cardiac function on TTE or CMRI.
Probable acute myocarditis	In the clinical context of possible of myocardial injury with cardiovascular symptoms and at least one of the following: biomarkers of cardiac injury raised; ECG findings suggestive of cardiac injury; abnormal cardiac function on TTE or CMRI
Definite myocarditis	Histological or immune-histological evidence of myocarditis

Diagnosis of myocarditis by CMRI (original and revised Lake Louise Criteria)[246]

In the setting of clinically suspected myocarditis, CMRI findings are consistent with myocarditis if two of the following are present: 1. Regional or global myocardial signal intensity increase in T2 weighted images 2. Increased global

myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1 weighted images 3. Areas with high signal intensity in a nonischemic distribution pattern in LGE CMRI
Revised Lake Louis Criteria
CMRI findings are consistent with myocarditis if the following criteria are met: 1. Regional or global myocardial signal intensity increase in T2 weighted images or increase in the myocardial T2 relaxation time AND one of the following two criteria: 2. The regional or global increase of the native myocardial T1 relaxation time 3. Areas with high signal intensity in a nonischemic distribution pattern in LGE images.

5) Cardiac sarcoidosis versus ACM[247]

Sarcoidosis is a multisystem idiopathic granulomatous characterized by noncaseating granulomas in involved organs. Organs involved with sarcoidosis include lymph nodes, skin, lung, central nervous system, eyes and heart. Only 40-50% of patients with cardiac sarcoidosis diagnosed at autopsy have the diagnosis made during their lifetime. Cardiac sarcoidosis can manifest itself as complete heart block, ventricular arrhythmias, CHF, pericardial effusion, pulmonary hypertension, and ventricular aneurysms. Diagnostic tests such as the ECG, TTE, CMRI, positron emission tomography scan, radionuclide scan, and EMB can be helpful in the early detection of this entity. Considering the increased risk of SCD, cardiac sarcoidosis is an indication for early treatment with corticosteroids or other immunosuppressive agents. Other treatments include placement of a pacemaker or ICD to prevent SCD. In refractory cases, cardiac

transplantation should be considered. The table shows the main features for the differential diagnosis between cardiac sarcoidosis and ACM.

Patients with cardiac sarcoidosis may present with clinical and morphological features similar to ACM or cardiomyopathy.[248] Sarcoidosis is an a chronic noncaseating granulomatous disease of unknown cause, characterized by multisystemic involvement. Practically no organ is immune to sarcoidosis; most commonly, in up to 90% of patients,

it affects the lungs.[249] The most commonly involved organ in sarcoid related death has been reported to be the lung in western countries, while it was the heart in the Japanese autopsy series.[250]

The diagnosis of myocardial sarcoidosis is difficult and frustrating. Its clinical manifestations depend on the location and extent of granulomatous inflammation, and the symptoms and signs range among benign arrhythmias, heart block, intractable CHF, intense chest pain, to fatal VF.[251]

The ECG may be normal or reflect every degree of block of the atrioventricular junction and bundle of His and every type of arrhythmia along with nonspecific ST-T-wave changes.[252] Other common ECG findings are signs of hypercalcemia (e.g. decreased QT interval), PR depression caused by pericarditis, or ST elevation caused by ventricular aneurysm. PVCs and NSVT are also common, seen by ECG in as many as 22% of patients with sarcoidosis. Sudden death from ventricular tachycardia and heart block accounts for up to 65% of deaths from cardiac sarcoidosis.[253]

Cardiac sarcoidosis should be considered in all young patients with unexplained conduction disorders,[254] CHF or in cases of SCD.[255]

In extensive forms are frequently pseudo myocardial infarction patterns with pathological Q waves on ECG.[256]

CMRI abnormalities, consisting of cardiac signal intensity and thickness, with the following three patterns: nodular; focal increase in signal on gadolinium diethylenetriamine pentaacetic acid-enhanced, T1-weighted images; focal increased signal on T2-weighted images without gadolinium uptake.

The improvement or stability of the MRI findings is correlated with clinical features.

With corticosterotherapy, the CMRI images improved either partially or completely, whereas.

The CMRI may find its usefulness as a guide to obtaining EMB specimens and to monitoring the response of the disease to treatment.

The study is small and lacks a correlation of myocardial histology with CMRI features. However, the study clearly calls for a large multicenter trial.[257]

The most significant drawback of CMRI is that the patient with a pacemaker and/or automatic ICD will not be able to take advantage of it. In such patients, 201Tl scanning remains the test for assessing myocardial damage.

Cardiac PET using F-FDG under fasting conditions is a promising technique for identification of cardiac sarcoidosis and assessment of disease activity. The metodology can detect the early stage of cardiac sarcoidosis, in which fewer perfusion abnormalities and high inflammatory activity are noted, before advanced myocardial impairment. The

sensitivity of fasting FDG PET in detecting cardiac sarcoidosis was 100%, significantly higher than that of 99mTc-MIBI SPECT (63.6%) or Ga scintigraphy (36.3%).

The accuracy of fasting FDG PET was significantly higher than Ga scintigraphy.[258]

An EMB is preferable, but the procedure has sensitivity as low as 20%.[259] Other authors referred sensitivity approximately of 50% thus, the search for a safe, reliable, and easily available diagnostic test for cardiac sarcoidosis continues. The pathological feature is the presence of noncaseating granulomas that eventually form fibrotic scars. Table 1 shows the main differences between the two entities.

	Cardiac sarcoidosis	**ACM**
Family history	Absent	Present in 30% to 50% of cases. When the disease is identified, genetic screening should be conducted among 1st degree relatives
Gender (M/F)	1 to 1	2.9 to 1
Mean age of presentation	Young people or adults in intermediary age	Adolescents and young adults. Rarely in children.
Multi-systemic involvement	Yes	No
Precordial pain	Intense precordial pain is described	No

Clinical manifestations of restrictive cardiomyopathy	Possible	No
Mitral valve insufficiency	Common	Only lately when it involves the LV.
ECG pattern of pseudo infarction	Frequent in extensive forms	No
PR interval duration	Longer	Shorter
Advanced atrioventricular block (AVB),	More frequent	Lesser frequent
QRS duration	Longer	Shorter
Peripheral TWI		favor a diagnosis of hereditary ARVC.
LV involvement	More extensive	Less extensive
RV apical involvement	Frequent	Rare
RVOT dimensions	Smaller	Larger
18F-FDG PET scan	Positive	Negative
Chest X-rays	Bilateral hiliar lymphoadenopathy.	Possible right cardiomegaly.
Pulmonary involvement	Present in >90% of cases. Frequent COPD.	No

Pathological anatomy	Non-cancerous granulomas that sometimes form fibrotic scars.	RV fibro-fatty substitution in the triangle of dysplasia.
Cardiac location involved more frequently	LV free wall and interventricular septum.	RVOT, RVIT and RV apex.
Pericardial effusion	Frequent	Absent
Improvement of symptoms shown by MNR with use of corticoids	Yes	No
Corticosteroids, chloroquine, methotrexate or cyclophosphamide	Sometimes prescribed	No
Sub tricuspid involvement	No	Frequent

Table X. Differential diagnosis between cardiac sarcoidosis and ACM.[260]

RVOT dimensions, subtricuspid involvement and peripheral TWI favor a diagnosis of hereditary ARVC.

6) Coronary artery disease (CAD) and myocardial infarction

CAD, or atherosclerotic narrowing of the coronary arteries, may lead to acute or chronic ischemic conditions that may mimic aspects of ACM. Clinical testing may be useful to distinguish CAD from ACM.

7) ACM versus congenital Heart Disease CHD

ACM eventually cause SCD in youth, which indicates the importance of diagnosis in its early stage. Additionally, tends to be confusing when it combines with some diseases that may also lead to RVH, making the diagnosis more challenging. ACM can accompany with congenital heart disease; in such occasion, careful differential diagnoses are required. Only few cases were reported as congenital heart disease combined with ACM; so the summary of the clinical features of these cases may provide a great reference for further practice.[261]

Congenital Heart diseases

7a) Uhl's anomaly or parchment heart vs ACM

	Uhl's	**ACM**
Family history	No	Yes
Inheritance pattern	Rarely familial	Most AD, some AR, *Compound Heterozygosity or Digenic Mutations.*
Pathogenic mechanism	Apoptotic dysplasia with complete absence of the myocardium.[262]	Apoptotic dysplasia of the myocardium followed by fibrofatty infiltration

SCD	No	Frequent in competitive Athletes
Associated lesions	1-4%	No.
Age at presentation	Usually diagnosed in neonatal or infant life	Young adult. rarely manifest symptoms before the age of 20 years, and usually present with palpitations or else die suddenly.
	Complete absence of the myocardium of the parietal wall of the RV. No fatty tissue interposed between these layers.	Fibro-fatty tissue replacement of the parietal wall of the RV.
Disease progression	Does not progress	Progressive postnatal development
Manifestation and evolution	Cyanosis, dyspnea, RV dilatation, CHF picture	From asymchst pain, asymptomatic, palpitations, atypical chest pain, syncope, SCD. Heat failure,

Uhl's anomaly is usually diagnosed in neonatal or infant life and present with CHF. It is a very rare congenital abnormality characterized by the almost complete absence of the myocardium in the RV which develops a parchment like appearance with associated diminution of function. It was first described in 1952 by Henry Uhl after performing an autopsy on an 8-month-old infant,[263] and it is thought that fewer than 50 cases have since been described. During embryonic development the human heart advances through phased embryological processes. It is thought that loss of the RV myocardium must only occur after complete cardiac development. Apoptosis is a routine component of postnatal morphogenesis of the human heart and it has been speculated that unrestrained RV myocardial apoptosis may be responsible.[264] With advancing imaging capabilities, now exemplified by CMRI, the diagnosis can be made more readily providing an opportunity to intervene surgically. Patients often present in infancy and rarely survive to adulthood without intervention. The typical imaging findings consist of a thinned, akinetic RV wall in association with a paucity of trabeculation with a dilated RV cavity.[265]

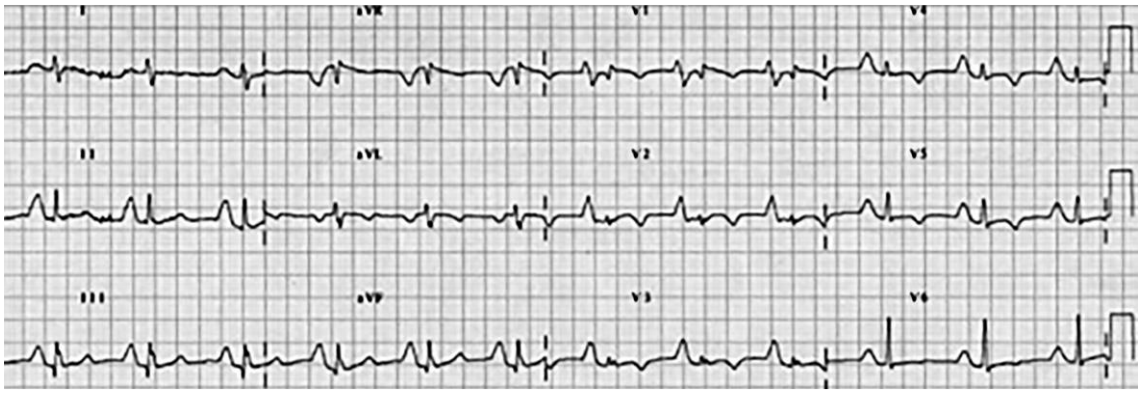
A 20-year-old Caucasian man was admitted to the emergency department with abdominal pain and worsening dyspnea, with 6 months of symptom evolution. He was class I or II NYHA, with no history of chest pain, palpitations, or syncope.

He had no relevant medical history and an unknown family history because he was adopted.

Physical examination revealed tachypnea with peripheral cyanosis, a pulse rate of 100 beats/min, normal blood pressure, apyrexia, and oxygen saturation of 95% on room air. The patient had jugular venous distension of about 8 cm at 45°, with

hepatojugular reflux. Pulmonary auscultation was normal, and a grade VI holosystolic murmur in the left sternal margin was present on cardiac auscultation. The abdomen was diffusely painful, and the liver edge was palpable 5 cm below the right costal margin.

Chest radiography showed cardiomegaly with a normal pulmonary vasculature pattern.



Sinus rhythm, HR 56 bpm, giant P wave (Himalayan P waves): tall (>5 mm) and peaked, most prominent in lead II, SÂP +75°, prolonged P duration (175 ms), P voltage from V1-V4 >QRS amplitude (small QRS amplitude from V1 to V4): QRS complexes of low voltage in V1 contrasting with QRS complexes of normal voltage or increased in V2 (modified Peñaloza and Tranchesi sign). In the present case small QRS complex form V1 to V3 contrasting with giant P waves, SÂT +90º (Figure X), TWI from V1 to V5.

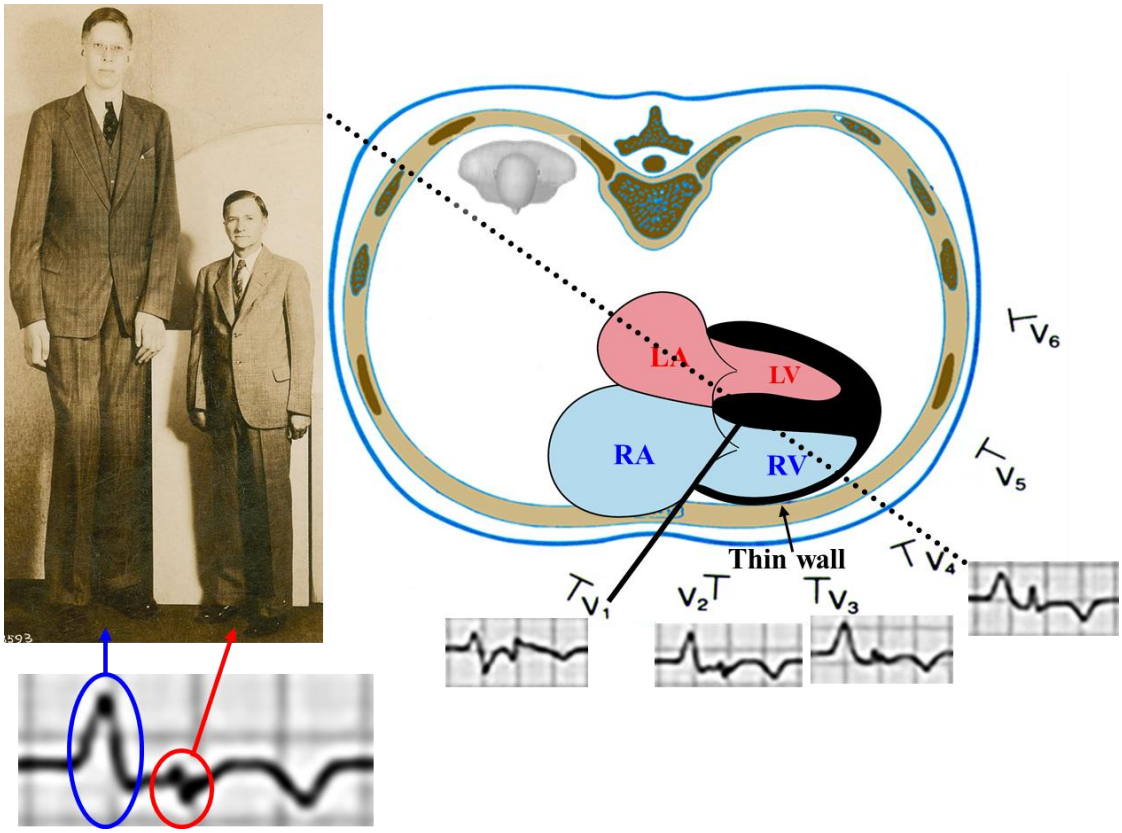


Figure X. Hypothetical contrast-voltage among giant P waves and small QRS complexes in the right precordial leads in the presence of Uhl's anomaly or parchment heart. The extremely thin free wall of the RV is almost unable to produce electrical potentials on the ECG with minimal QRS amplitude in the right precordial leads which develops a parchment-like appearance associated with diminution of function. The real cause of small QRS complexes from V1 to V3 is the absence of myocardium in the RV parietal wall.

Table X shows the differential diagnosis between Uhl's anomaly and ACM.

	Uhl's anomaly	ACM
Family history	No	Yes
Sex ratio	1:1	Polemic, conflict data

SCD	No	Frequent in competitive Athletes
Associated lesions	1-4%	No
Age of presentation	Usually diagnosed in fetus, neonatal or infant life	Young adult, symptoms rarely manifest before the age of 20 years, and usually present with palpitations or SCD.
	Complete absence of myocardium in the RV parietal wall. No fatty tissue interposed between these layers.	Fibro-fatty tissue replacement in the RV parietal wall.
TVI	Possible	TWI in the right precordial leads from V1 to V3 or beyond, aged >14 years of age, without complete RBBB
Epsilon waves	Prominent ε waves in all QRS complexes	

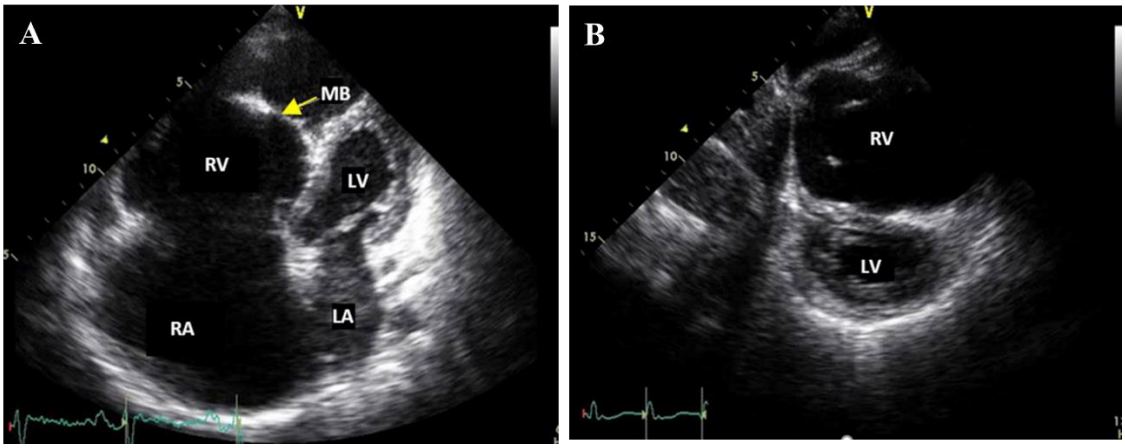


Figure. (A) Transthoracic echocardiogram(TTE), apical four-chamber view in diastole, showing marked right atrial and right ventricular dilatation. A moderator band (MB) and thin right ventricular walls were observed. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (B) TTE, parasternal short-axis view in diastole, showing marked RV dilatation with thin walls and interventricular septum flattening. LV, Left ventricle; RV, right ventricle. TTE shows marked RV dilatation with thin walls (1–2 mm in almost all regions) and significant depression of its contractility. Right atrial enlargement is also observed, as well as hypertrophy with normal left chambers. The tricuspid valve has normal morphology and implantation.

Figure X

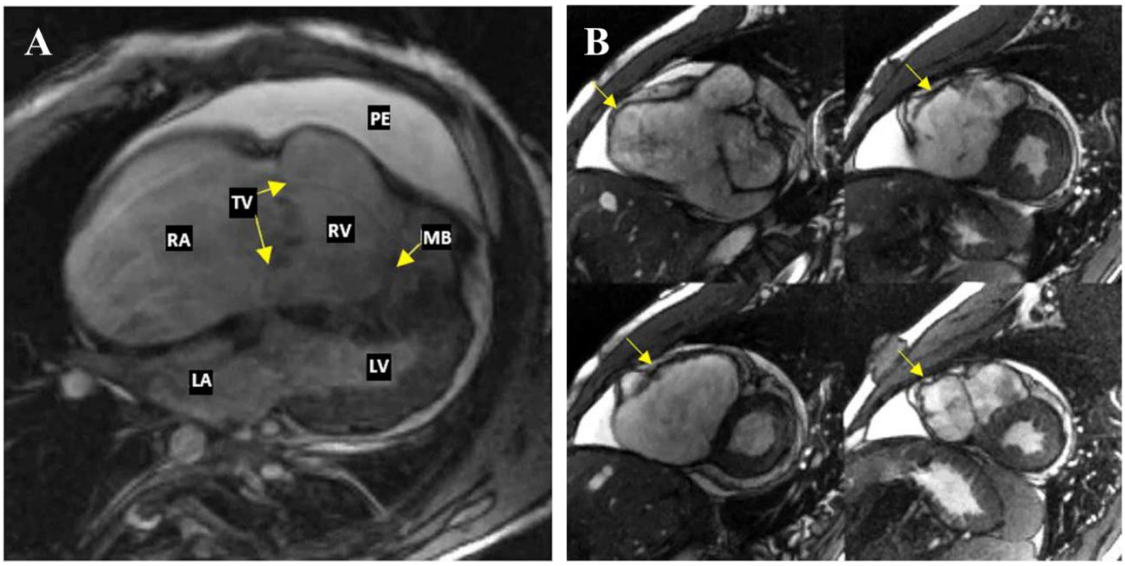


Figure X. (A) Cardiac magnetic resonance image(CMRI), in steady-state free precession, four-chamber sequence showing marked right chamber dilatation. The tricuspid valve (TV) has normal positioning. A moderator band (MB) and a medium-volume pericardial effusion (PE) are visualized. LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle. Cardiac magnetic resonance imaging reveals an extremely thin-walled right ventricle with almost complete absence of free wall myocardium and with scarce apical trabeculations. There is no fibrofatty infiltration, with RV systolic dysfunction. (B) CMRI, in steady-state free precession, short-axis sequence showing normal left ventricular size, and the obvious thinning of the RV free wall (arrows).

Uhl's anomaly is usually diagnosed in neonatal or infant life and present with CH. It is a very rare CHD congenital abnormality characterized by the almost complete absence of the myocardium in the RV which develops a parchment like appearance with associated diminution of function. It was first described in 1952 by Henry Uhl after performing an autopsy on an 8-month-old infant,[263] and it is thought that fewer than 50 cases have since been described. During embryonic development the human heart advances through phased embryological processes. It is thought that loss of the RV myocardium must only occur after complete cardiac development. Apoptosis is a routine component of postnatal morphogenesis of the human heart and it has been speculated that unrestrained RV myocardial apoptosis may be responsible.[264] With advancing imaging capabilities, now exemplified by CMRI, the diagnosis can be made more readily providing an opportunity to intervene surgically. Patients often present in infancy and rarely survive to adulthood without intervention. The typical imaging findings

consist of a thinned, akinetic RV wall in association with a paucity of trabeculation with a dilated RV cavity.[265]

In 1979, Fontaine *et al*[266] described ACM, characterized by fibrofatty replacement of the RV myocardium.

Gerlis *et al* concluded that many cases of ACM were incorrectly classified as Uhl's anomaly, and these two entities had to be distinguished.[262, 267]

Other congenital heart diseases

7b) Repaired tetralogy of Fallot[268]

7c) Ebstein's anomaly

7d) Atrial septal defect (ASD)

7e) Partial anomalous venous return

7f) Tricuspid valve disease

8) **ACM and anterior polar cataract (APC**). A single family with ACM and subscapular cataract, a rare hereditary form of lens opacity, has been described.[269] The proband and his sister both had ACM and APC. The gene responsible for APC previously was linked to 14q24qter. Parents of the sibs were second cousins (OMIM 115650).

Pathogenic variants in DES have been associated with: The phenotype of skeletal myopathy, dilated cardiomyopathy, and ACM (per the 1994 ACM diagnostic criteria) in families;[78, 80] Skeletal myopathy (OMIM PS601419) or dilated cardiomyopathy with or without cardiac conduction defects;[270, 271]

Comparison of characteristics between ARVC patients with and without the Brugada pattern on ECG

Clinical characteristics	**All**	**Brugada pattern (+)**	**Brugada pattern (−)**	***P* value**
Prolonged TAD, n (%)	72/92 (78)	2/2 (100)	70/90 (78)	.32
ε wave, n (%)	23 (20)	2 (40)	21 (19)	.30
J wave, n (%)	17 (15)	1 (20)	16 (15)	.75
Positive in SAECG, n (%)	102/111 (92)	4/4 (100)	98/107 (92)	.41
EPS inducibility, n (%)	60/91 (66)	3/3 (100)	57/88 (65)	.11
Fibrofatty replacement of myocardium on EMB, n (%)	52/82 (63)	3/4 (75)	49/78 (63)	.61
Amiodarone, n (%)	36 (32)	2 (40)	34 (31)	.68
Sotalol, n (%)	21 (18)	2 (40)	19 (17)	.25
β-blockers, n (%)	60 (53)	0 (0)	60 (55)	.0054
Family history of ARVC, n (%)	3 (3)	0 (0)	3 (3)	.60

Values are presented as mean ± SD, median (interquartile range), or n (%).ARVC, arrhythmogenic right ventricular cardiomyopathy; BSA, body surface area; CRBBB, complete right bundle branch block; ECG, electrocardiogram; EMB, endomyocardial biopsy; EPS, electrophysiological study; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRI, magnetic

resonance imaging; rTFC, revised Task Force Criteria; RV, right ventricular; RVEF, right ventricular ejection fraction; SAECG, signal-averaged electrocardiogram; TAD, terminal activation duration.

The impact on the changes in autonomic tone or heart rate will be valuable in identifying the differences in ECG characteristics between ARVC and BrS. Further investigation is necessary to understand the mechanism of characteristic J-ST elevation in ARVC and BrS.

The significance of ECG in the diagnosis and risk assessment of ARVC was reported by Alencar Neto and Bayés de Luna. (**Alencar N, Neto J, Baranchuk A, Bayes-Genis A, Bayes de Luna A. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: an electrocardiogram-based review. *Europace*. 2018; 20: f3– f12**.). They also mentioned that specific ECG findings in ARVC patients should be carefully evaluated because of high interobserver variability and disagreement between experts. Thus, extreme care should be taken in ECG analysis in patients with ARVC.

Limitations

This was a single-center, retrospective study. The relatively small number of ARVC patients may therefore limit the interpretation of these results. Moreover, because of the low incidence of a positive Brugada-type ECG, the authors should be cautious with statistical interpretations and clinical utility. A sodium-channel blocker test was not performed to unmask the Brugada ECG pattern because of safety concerns. The additional recording of right precordial leads on the upper intercostal area was conducted in a small number of patients. Because daily and circadian fluctuation of J-ST morphology is common in BrS and the Brugada ECG appeared transiently, there is a possibility that the detection rate was underestimated. The number of patients who underwent genetic testing for ARVC was low, and no ARVC patients with a Brugada ECG pattern underwent genetic analysis. Some ECGs with the Brugada pattern in ARVC patients showed an unrepresentative configuration for BrS patients. The mechanism of the Brugada ECG pattern was not evaluated and the association with repolarization

abnormality was unclear. Further prospective, multicenter studies, which include a larger number of ARVC patients, are warranted to confirm these findings.

Ueda et al concluded that in ARVC patients, the Brugada ECG pattern was infrequently encountered. This pattern appeared transiently and disappeared during follow-up. A Brugada ECG pattern increased the risk of cardiac death and HF hospitalization in patients with ARVC.

I) Geographic distribution/ predilection

a. **ACM:** Worldwide. Italy/Padua. Naxos island AR variant. The non desmosomal gene TMEM43-endemic to Newfoundland, Canada. To date, all familial cases reported worldwide share a common ancestral haplotype.[75] The entity had been associated with the Mediterranean region, as many seminal studies had originated from research groups in France, Greece, and Italy. Today, however, numerous worldwide registries emphasize that the disease does not have a specific racial or geographical predilection.[272]

b. **BrS:** Endemic in Southeast Asia such as Thailand (*Lai Tai*).[273] *Lai Tai* is ≈30 cases per 100,000 population per year. Philippines (*Bangungot*),[274] Japan (*Pokkuri*).[275]

II) Inheritance Pattern

a. **ACM:** AD, AR, *Compound Heterozygosity or Digenic Mutations*

b. **BrS:** AD manner. In about 1% of cases, an affected person has a new mutation in the responsible gene and has no family history of the condition. TRPM4 mutations (transient receptor potential cation channel subfamily M member 4) cause AR and not AD Brugada

syndrome (Red list: low evidence) This gene is also associated with Progressive familial heart block, type IB 604559

III) Family history

a. **ACM:** ACM confirmed in a first-degree relative who meets current TFC; ACM confirmed pathologically at autopsy or surgery in a first-degree relative Identification of a pathogenic mutation categorized as associated or probably associated with ACM in the patient.

b. **BrS:** Family history of SCD is not predictive for future arrhythmic events even if considering only SCD in first-degree relatives or SCD in first-degree relatives at a young age. The absence of syncope, aborted SCD, spontaneous type I ECG, and inducibility during EPS is associated with a good five-year prognosis.[276]

IV) Prevalence

a. **ACM:** The estimated prevalence of ACM in the general population ranges from 1 in 1,000 to 1 in 5,000.[194] Peters refers as 1:1,000 to 1: 1,250.[33] or 1:2,000–1:5,000.

b. BrS: The highest prevalence was reported in Southeast Asian countries such as Thailand, the Philippines, Japan, and Singapore (1.8 per 1,000)[277] But this number varies from geographic differences that ranges from 0.5 to 4 per 1,000 in those countries.[278, 279] The lowest was found in North Africa (0 per 1,000). BrS in Asians was 9 times more common than in Caucasians and 36 times more common than in Hispanics. The worldwide pooled prevalence of Type-2 Brugada pattern was 6.1 per 1,000. The highest prevalence was also reported in Southeast Asia (35.5 per

1,000, 95% CI: 17.1-53.9).[280] The prevalence is estimated to range between 1 in 5,000 to 1 in 2,000 in different populations, but less than 0.2 per 1,000 in the western hemisphere.[281]

V) Gender differences

a. **ACM:** M/F ratio: 3:1[197] sex-based differences in the incidence are conflicting. Italian studies report that it is more common in males with an approximate ratio of 3:1,[37] on the other hand the United States and the Dutch ACM cohorts report similar incidence between males and females.[3, 38] European studies (predominantly from the Netherlands) and the United States show that AMC is 1.2–3 times more common in males.[3, 38, 90, 198, 199] However, the male predominance is not observed in USA Registry (89% of males vs. 84% of females).

b. **BrS:** M/F ratio: 8:1. Female sex decreases risk.[282, 283] Sinus node dysfunction in females increases risk.[284] Female patients with BrS are much rarer, display less type 1 Brugada ECG pattern, and lower inducibility rates than in males. Finally, patients with BrS with AEs have higher SCN5A mutation rates as well as the relationship between gender vs age at the onset of AEs and ethnicity.[285]

VI) Predominant gene mutation

a. **ACM:** Mutations in a desmosomal PKP2 gene appear to be most common. Heterozygous mutation in PKP-2, encoding Plakophilin-2 protein, is the commonest cause of ACM.[106, 286, 287]

b. **BrS:** The underlying genetic cause of inherited forms of BrS is not known in most cases, but in up to 20-30% of people with BrS, it is

caused by a mutation in the *SCN5A* gene.[288] BrS with SCN5A mutation is considered the BrS-1 [289] with **Cytogenetic location**: 3p21-23; OMIM: 601144. The Ion channel and effect: INa+ loss-of-function; Protein: NaV1.5 - α subunit of the cardiac sodium channel carrying the sodium current INa+; % of probands: 11-28%. Amin et al [290] hypothesized based on a study of AF in a large cohort of BrS patients, that a reduced number of potentially triggering premature atrial contractions (PACs) in the presence of a more extensive substrate in SCN5A mutation carriers may account for AF being no more prevalent in patients with SCN5A mutations than in those without. Given the polemic and complex issues underlying the pathophysiology of BrS, one should regard this hypothesis as one potential mechanism of many that influence the prevalence of AF in BrS. Mutations in SCN5A lead to a broad spectrum of phenotypes, however the SCN5A gene is not commonly involved in the pathogenesis of BrS and associated disorders. Studies have revealed significant overlap between aberrant rhythm phenotypes, and single mutations have been identified that evoke multiple rhythm disorders with common gating lesions. Nav1.5 consists of peak and late components (INa-P and INa-L). Mutant Nav1.5 causes alterations in the peak and late Na+ current and is associated with an increasingly wide range of genetic arrhythmias. More than 400 mutations have been identified in the SCN5A gene. Although the mechanisms of SCN5A mutations leading to a variety of channelopaties can be classified according to the alteration of

INa-P and INa-L as gain-of-function, loss-of-function and both, few researchers have summarized the mechanisms in this way.[291] Gain-of-function mutations in SCN5A lead to more Na+ influx into cardiomyocytes through aberrant channel gating causing LQT3. Slowed or incomplete inactivation of the NaV1.5 channel results in an additional inward current, known as the late or persistent sodium current (Ipst), during the plateau phase of the ventricular action potential with ST segment prolongation and late T occurrence. Among the mutations in SCN5A associated with LQT3 is 1795insD, which is characterized by the insertion of 3 nucleotides (TGA) at position 5537 C-terminal domain of the NaV1.5 protein.[292] Carriers of this mutation may not only present with LQT3, but also with ECG features of sinus bradycardia, progressive cardiac conduction disease, and Brugada syndrome, thus creating the first described arrhythmic 'overlap syndrome'.[293] Interestingly, 1795insD is supposed to be a gain-of-function mutation in light of the QT prolongation, but a loss-of-function mutation in light of the sinus bradycardia, progressive cardiac conduction disease, and BrS. Additionally, and multifocal ectopic premature Purkinje-related complexes; loss-of-function mutations in SCN5A result in amplitude reduction in peak Na+ current, further leading to channel protein dysfunction. i or cardiac conduction defect an entity with minor SHD. In addition, both loss- and gain-of-function mutations may cause dilated cardiomyopathy and/or AF.[294] On ECG PR interval prolongation is the only parameter that predicted the presence of a

SCN5A mutation in BrS, additionally, late potentials on high resolution ECG LP were more frequently observed in SCN5A mutation carriers.[295] SCN5A mutation is associated with an increased risk of drug-induced ventricular arrhythmia in patients without baseline type-1 ECG. In particular, Snon-missense and Smissense-TP are at high risk.[296]

VII) Ethnic differences

- **ACM:** In the first to comprehensively evaluate genetic variation in healthy controls for the ACM susceptibility genes. Radical mutations are high-probability ACM -associated mutations, whereas rare missense mutations should be interpreted in the context of race and ethnicity, mutation location, and sequence conservation.[111]
- **BrS**: There are marked differences between Asian and Caucasian patients with BrS. Asian patients present almost exclusively as male adults, more often with aborted CA and spontaneous type 1 BrS-ECG. However, they have less family history of SCD and markedly lower SCN5A mutation rates. The striking difference in SCN5A.[297] SCN5A mutations in BrS increase the risk of MAE in Asians, symptomatic BrS patients, and individuals with spontaneous type-1 Brugada pattern. Positive SCN5A mutation should be considered an important tool for risk in BrS patients.[298]

VIII) Penetrance/expressivity

- **ACM:** Incomplete penetrance and variable expressivity are the hallmark,[36] reviewed the genetics of ARC, noting that in 35 to 40%

of patients, no causal mutation had been identified. The phenotypic penetrance is variable and is strongly related to the amount of exercise. Endurance exercise level has impact in this.

- **BrS:** Incomplete Penetrance and variable Expressivity: hallmarks in channelopathies associated with SCD.[299]

IX) Predominant gene mutation

- **ACM:** Gene mutations have been found in about 60 percent of people with ACM. Mutations in a desmosomal gene plakophilin-2 (PKP2) appear to be most common. Of patients with PKP2 genetic variants, 25 of 38 (65.7%) were found to have a second PKP2 abnormality or a second abnormal desmosomal gene.[130] In people without an identified mutation, the cause of the disorder is unknown. Researchers are looking for additional genetic factors that play a role in causing ACM.
- **BrS:** SCN5A gene encoding the pore-forming α-subunit of the cardiac sodium channel protein.

X) Main complains and clinical presentation

- **ACM** should be suspected if the following symptoms occur, particularly in young athletes: palpitations (feeling your heart beating too fast, too hard or like it is 'fluttering') – this is caused by arrhythmias (when the electrical messages which control the heart's rhythm are disrupted), cardiogenic dizziness, arrhythmic (pre)syncope (light-headedness and fainting) – reduced oxygen levels or blood flow to the brain, due to arrhythmias, can cause light-headedness or dizziness and, in some cases, loss of

consciousness), aborted SCD or CA, chest pain, swollen legs, ankles and tummy – build-up of fluid in the tissues, because the heart is not pumping effectively, can cause swelling (called 'oedema'), breathlessness or dyspnea – fluid builds-up around the lungs, making it harder to breathe, ± rise in cardiac biomarkers, presumed DCM with early onset and frequent ventricular arrhythmias, precordial TWI inversions beyond V1 after puberty, progressive CHF.

- **BrS:** arrhythmic syncope (fainting),[300] CA, or SCD. Unexplained nocturnal death syndrome because people with it can often die in their sleep or at rest or occasional palpitations, chest pain,[301, 302] and fever-induced expression of BrS phenotype in children,[303] breathlessness, or dizziness.

XI) Events circumstance

- **ACM:** During exercise. ACM accounts for up to 20% of cases of SCD in young athletes.[204, 205]
- **BrS:** At rest or during sleep 80% of cases. The triggers for cardiac events and precipitating factors for fatal arrhythmias (ie syncope or CA) and SCDs include exercise, fever, ischemia, bradycardia, electrolyte disturbances, and non-recommended drugs use such as cocaine, anesthetics, antiarrhythmic agents, antidepressants, and antihistaminic agents).

XII) Electrocardiographic features

a. Repolarization abnormalities

- **ACM:** 1) TWI in V1, V2 and V3.; 2) Down sloping elevated ST-segment pattern in V_1 and V_2 occurs with more unipolar endocardial voltage abnormality, consistent with more advanced transmural disease.[304]
- **BrS:**
  - **Inferolateral early repolarization pattern**. J wave > 0.1 mV in at least two inferolateral leads increased risk[305] (conflicting data).
  - **T-Wave Alternans (TWA)** in an experimental model transmural dispersion of repolarization of the BrS is due to alternating loss of the epicardial AP dome and/or concealed phase 2 reentry, both serving to increase transmural dispersion of repolarization and create the substrate for the development VT/VF.[306] Sakamoto et al assessed TWA for risk stratification using 24-h multichannel Holter (24-M-ECG) in BrS. The authors enrolled 129 patients with BrS grouped according to histories of VF, n = 16; syncope, n = 10; or asymptomatic, n = 103 and 11 controls. Precordial electrodes were attached to the third (3L-V1, 3L-V2) and fourth (4L-V1, 4L-V2 and 4L-V5) intercostal spaces. They measured the values of maximum TWA (max-TWA) during the night time (12 a.m.–6 a.m.) and the day time (12 p.m.–6 p.m.) and calculated parameters of heart rate variability (HRV). Compared to the asymptomatic and control groups, the VF and syncope groups showed significantly greater 3L-V2 max-TWA during the night time. The cutoff value for the 3L-V2 max-TWA

during the night time was determined as 20 μV (sensitivity 94 % and specificity 48 %; p = 0.01). Multivariate analysis revealed that 3L-V2 max-TWA during the night time ≥20 μV and previous VF episodes were independent predictors of future VF episodes. During a mean follow-up period of 68 ± 37 months, 16 patients experienced VF episodes. The incidence of VF episodes was the highest during the night time. The 3L-V2 max-TWA during the night time may be a useful predictor for VF episodes in patients with BrS.[307] In BrS, sodium channel blockade provokes the diagnostic ECG changes as well as macroscopic TWA and arrhythmias. TWA after pilsicainide administration is associated with a high risk of clinical VF in patients with BrS.[308] Overall, although TWA appears to be a useful marker of risk for arrhythmic and cardiovascular death, however there is as yet no definitive evidence that it can guide therapy.[309]

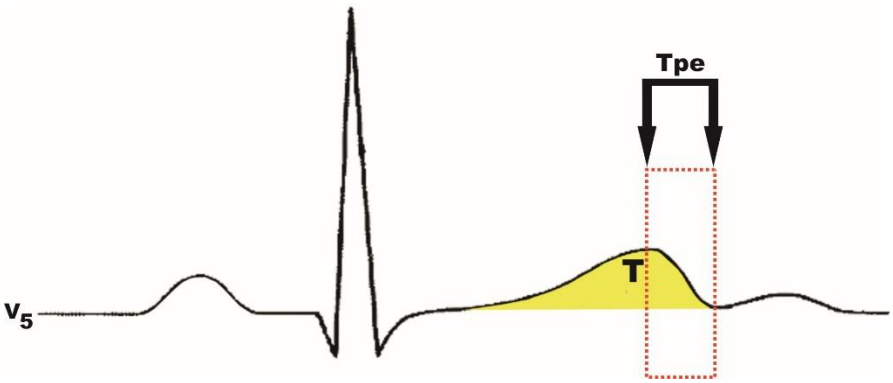
- **Post-exercise ST-segment elevation at the early recovery phase during Treadmill exercise testing increased risk:** Augmentation of ST-segment elevation during recovery from exercise testing was specific in patients with BrS, and can be a predictor of poor prognosis, especially for patients with syncope alone and for asymptomatic patients. This observation is promising but needs to be confirmed.[310] However, several points argue against embracing the exercise test as the main tool for defining the need for therapy among asymptomatic BrS patients: 1) the test failed to identify 68% of patients with a history of CA;

2) the reproducibility of the test was not tested; and 3) the study included only 36 patients with asymptomatic BrS, and that 8% of them had arrhythmic events during follow-up suggests that this was an a priori high-risk population (for comparison, 2% of initially asymptomatic patients had symptoms in the 2 multicenter studies already noted).[311, 312] In the absence of well-established and reliable prognostic tests, Viskin, and Belhassen recommend prophylactic drug therapy with quinidine for asymptomatic BrS. It is, therefore, important to continue all efforts to prevent the disappearance of quinidine from the market.[313, 314] Exercise testing in asymptomatic patients with type 1 Brugada pattern aids in identification of high-risk patients and provides a unique window of opportunity for early intervention. Treadmill exercise testing was conducted by Subramanian et al in 75 asymptomatic patients with type 1 Brugada pattern and for 88 healthy controls. The clinical end point of MAE was defined as the occurrence of SCD or resuscitated VF. During a follow-up of 77.9 ± 28.9 months, eight MAE occurred (five VF and three SCD). Multivariate Cox regression analysis showed that the following were independent predictors of MAE in asymptomatic patients with a type 1 Brugada pattern: increase in S wave upslope duration ratio >30% at peak exercise, augmentation of J point elevation in lead aVR >2 mm in late recovery, and delayed HR recovery. A high-risk cohort was identified by the final step-wise regression model

with good accuracy (specificity = 98.4%, sensitivity = 62.5%) and discriminative power (AUC = 0.93, 95% CI 0.89-0.96, P = 0.002). Kaplan-Meier analysis revealed increasing MAE in subjects with one, two, or three predictors, respectively.[315] Morita et al. with the objective of determine the significance of exercise-related PVCs for predicting occurrence of VF in patients with BrS. They studied 307 patients with BrS who performed a treadmill exercise test. They evaluated the occurrence of PVCs at rest, during exercise and at the peak of exercise, and during recovery after exercise (0-5 minutes). They followed the patients for 92±68 months and evaluated the occurrence of VF. PVCs occurred in 82 patients (27%) at the time of treadmill exercise test: PVCs appeared at rest in 14 patients (4%), during exercise in 60 patients (20%), immediately after exercise (0-1.5 minutes) in 28 patients (9%), early after exercise (1.5-3 minutes) in 18 patients (6%), and late after exercise (3-5 minutes) in 12 patients (4%). Thirty patients experienced VF during follow-up. Multivariable analysis including symptoms, spontaneous type 1 ECG, and PVCs in the early recovery phase showed that these factors were independently associated with VF events during follow-up. The significance of exercise test–induced PVCs has not been recognized in patients with BrS. Patients with PVCs during early recovery phase after an exercise test frequently experienced VF during follow-up. PVCs during the early recovery phase (1.5–3 minutes) after an exercise test by vagal

rebound can identify the high-risk patients with BrS. Exercise tests are safe because they do not induce VF in patients with BrS. Exercise tests can be a useful risk stratification tool for predicting future occurrence of VF in patients with BrS. In conclusion PVCs early after an exercise test are associated with future occurrence of VF events. Rebound of vagal nerve activity at the early recovery phase would promote ST-segment augmentation and PVCs in high-risk patients with BrS.[316] There are insufficient data on the risks of exercise in BrS to make recommendations for exercise, but the observations that exercise can worsen the ST abnormalities in BrS and produce ventricular arrhythmias suggest that patients with BrS should be restricted from vigorous exercise.[317]

- **Prolonged T-Peak-T-end interval:** Increased risk, but needs to be confirmed.[318] The normal value of Tpeak/Tend interval (Tpe) is 94 ms in men and 92 in women when measured in the V_5 lead. Tpe prolongation to values ≥120 ms is associated to a greater number of events in patient's carriers of BrS.



Interval elapsed from the apex to the end of T wave (Tpeak-Tend interval or Tpe). Tpe may correspond to transmural

dispersion of repolarization and consequently, the amplification of this interval is associated to malignant ventricular arrhythmias.

a. ECG depolarization abnormalities

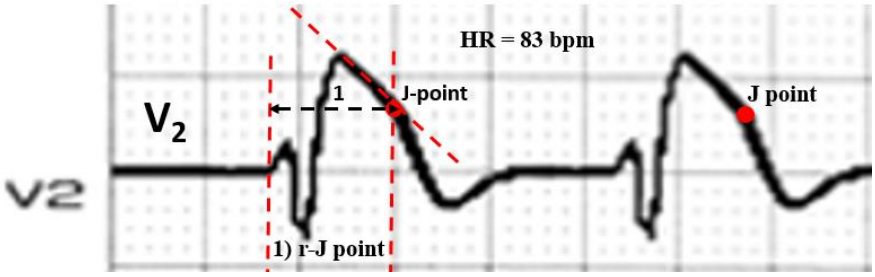
- **ACM:**
  - Right precordial QRS prolongation (>110 ms) of the QRS complex in right precordial leads (V1–V3).
  - Epsilon waves in the right precordial leads (**major criteria?**). Its identification and interpretation are influenced by ECG filtering and sampling rate, with large interobserver variability.[147] Consequently, currently Padua researches consider epsilon waves in right precordial leads a **minor ECG criterion**.
  - **12-lead surface ECG in classic right dominant form:** QRS prolongation in V1–V3: QRS delayed S wave upstroke with TAD ≥55 ms in right precordial leads in the absence of CRBBB. TAD is measured from the nadir of the S wave to the end of all depolarization.[319] ε wave in V1–V3, IRBBB, TWI in V1–V3, TWI in V1–V6 with biventricular involvement and poor precordial leads R wave progression.
  - **12-lead surface ECG in left dominant form:** Leftward QRS axis (<0°), early precordial R wave transition, ε-like waves in inferior or lateral leads, LBBB, TWI in inferolateral leads and TWI V1–6 with biventricular involvement.[163]

- **QRS fragmentation (fQRS)**: QRS fragmentation in the S wave of right precordial leads identifies patients with recurrent VT/VF, and recurrent ICD discharges. fQRS ≥3 leads characterized patients who died from SCD. Patients with recurrent VT who develop biventricular HF requiring heart transplantation and/or diuretics are characterized by fQRS in the S wave of right precordial leads and ≥3 of all 12 ECG leads. These results are statistically significant. Patients with initial RBBB have an overall benign prognosis.[320] Regression of fQRS could be a maker of electrical reverse remodeling following cardiac resynchronization therapy.[321]

- **BrS**

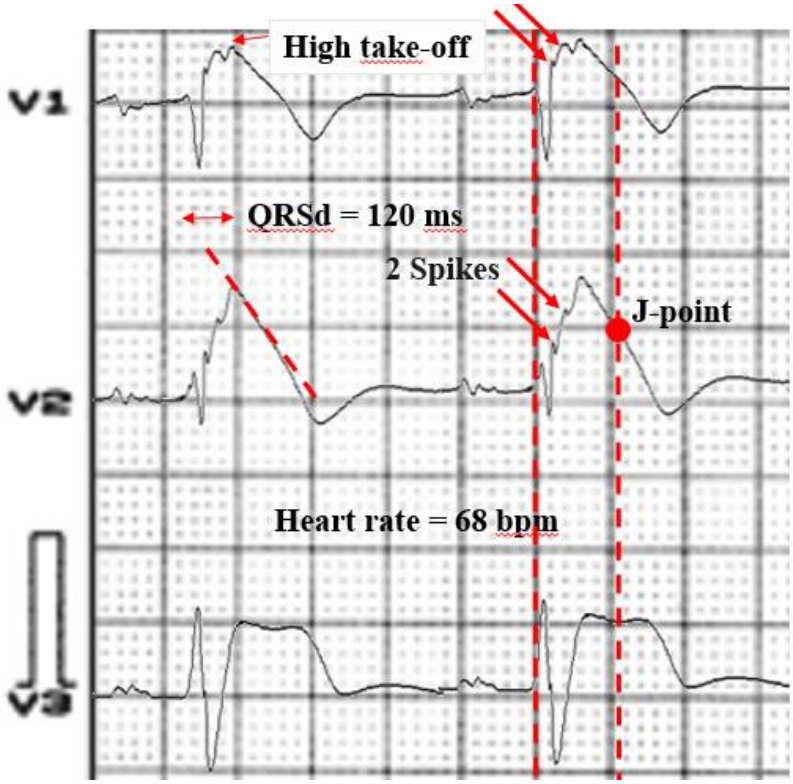
  a) **Prolonged QRS duration measured from lead II and/or lead V2 ≥120 ms.** Additionally, it is considered a risk marker[322] (Figure x).

  Prolonged QRS duration measured from lead II or lead V2 ≥120 ms



Vertical dotted lines show onset and termination of the QRS complex in V2. In this case QRSd = 165 ms. It is an ECG marker of events.

b) **QRS fragmentation (fQRS):** at least four spikes in one or at least eight spikes in all of the precordial leads. Presence of fQRS increase risk.[323] fQRS is known to be a marker of myocardial injury and conduction delay. fQRS in the right precordial leads represents electrophysiological abnormality of the RVOT and is associated with lethal arrhythmic events in patients with BrS. Epicardial mapping and RFCA showed delayed potential on the epicardium of RVOT. It is a substrate of ECG change and ventricular events in BrS. Additionally, it is also recorded outside of RVOT region. fQRS is observed with higher frequency of fQRS at the RVOT, followed by the inferior wall region and RV, and appearance of fQRS in any ventricular region was associated with occurrence of MACE in asymptomatic and symptomatic patients. Appearance of fQRS in multiple regions was associated with easily induced VF by PES and a marker of early occurrence of MACE.[324] Figure

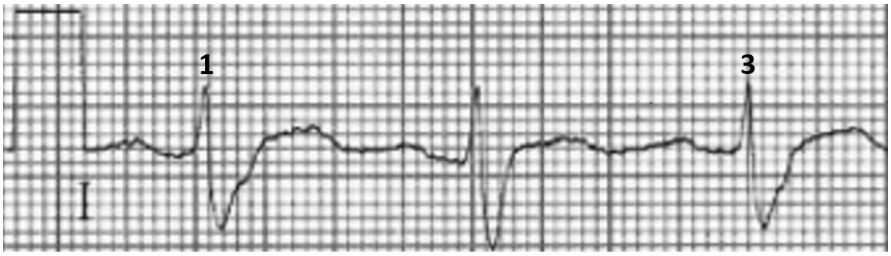


Spikes are registered at the upstroke of the S wave in leads V_1 and V_2.

c) **QRS complex duration (>110ms) in right precordial leads, in absence of CRBBB:** parietal block.[183]

d) **Coved and saddle-back types with day-to-day variation.** Right precordial high take-off ST elevation followed by TWI ("coved-type morphology") Type 1 Brugada pattern. The type 1 is required for the diagnosis of BrS whereas the significance of saddle-back type ECG (type 2), which is inadequate for the diagnosis, has not been fully established.[325]

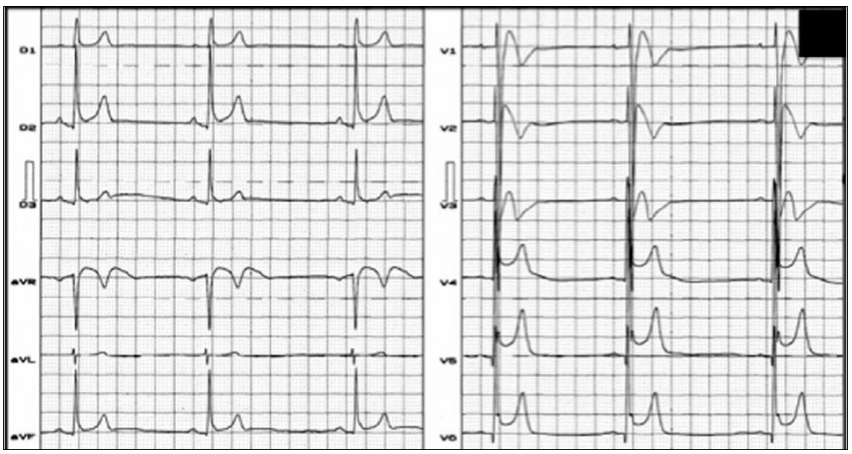
e) **S wave deep in lead I >0.1 mV and/or >40 ms duration increased risk: Caló sign.[326]**



Beats 1 and 3 have broader S wave related beat 2 consequence of higher degree of RBBB. The presence of a wide and/or large S-wave in lead I is a powerful predictor of life-threatening ventricular arrhythmias in patients with BrS and no history of CA at presentation. However, the prognostic value of a significant S-wave in lead I should be confirmed by larger studies and by an independent confirmation cohort of healthy subjects. This is the first time; that it is known to us that the Calò´s signal is observed intermittently or transiently.

f) **Type 1 Brugada pattern registered in the inferior leads increase risk in BrS patients**[327] (Figure).

Coexisting early repolarization pattern (ERP) and type 1 Brugada pattern: recognition of potentially overlapping entities.



Coexistence ECG that shows concomitant early repolarization pattern in inferior lateral leads associated with type 1 Brugada pattern in young soccer player Caucasian man.[328]

Atrioventricular conduction time affectation

- **ACM:** Fibrofatty infiltration of the bundle of His has been found in pathology studies in more than 60% of patients with ACM.[205, 329] Histological evidences do not correlate with conduction disturbances. Rarely ACM with conduction disturbances have been described in the literature.[330] Peters,[331] in 376 patients with ACM, found complete RBBB and any degree of atrioventricular block in 6% of cases.
- **BrS:** Progressive prolonged PR/HV interval[332] or Split-His.

The most common ventricular arrhythmias

- **ACM:** NSMVT or SMVT of LBBB morphology with superior axis (negative or indeterminate QRS in inferior leads, and positive in lead aVL) (major criteria). Frequent PVCs (1000/24h). **Minor criteria:** >500 PVCs per 24h-Holter.
- **BrS:** Arrhythmias in BrS patients originate in the RVOT. Polymorphic VT, VF, PVCs with short coupling. The LQTS, SQTS, BrS and CPVT are channelopathies with very different phenotypes and etiologies, but which share a common final pathway in causing SCD: selective abbreviation of the APD of right ventricular epicardium.[333] In channelopathies the predominant

ventricular events are PVTs, TdP and VF. In rare cases very fast MVT is registered. This is why ICDs should always be programmed for treatment of VF only with high detection heart rates to avoid inappropriate ICD discharges.[334]

Typical mechanisms of VT

- **ACM -** Two mechanisms are described: **Enhanced automaticity** with high prevalence in concealed and early ACM, characterized by fast self-terminating VT, onset during exercise, beta-blockade with high effective. **Scar mediated re-entry**, typical of established disease, characterized by recurrent SMVT. The approach is AAD or catheter ablation: pre procedure planning consisting in endo and epicardial access, creating a voltage map, producing induction of arrhythmias with high dose isoproterenolol, programmed stimulation, and mapping during VT (http://www.venicearrhythmias.org/wp-content/uploads/2015/05/H-Tandri.pdf).

- **BrS**: The current understanding of both ACM and BrS phenotypes hint toward a partial overlap in pathophysiological mechanisms causing structural abnormalities as in both entities, the RVOT is a unique structure in terms of anatomy and electrophysiology, which could explain why its preferential site of origin in the setting of BrS. Currently, the true answer remains obscure.[335]

Late potentials (LPs) on the signal-averaged ECG (SAECG)

- **ACM:** Late potentials are considered present if ≥1 of the following parameters are abnormal: total filtered QRS duration ≥114 ms, the low amplitude (<40 μV) late signal duration ≥38 ms, and the last (40 ms) QRS root-mean-square voltage ≤20 μV. **Observation:** LPs on SAECG are no longer included among the Padua criteria, since the use of SAECG technique has been abandoned by most centers because of its non - specific findings and limited diagnostic accuracy[146] (polemic).
- **BrS:** Recent study shows a high prevalence of SAECG abnormalities in children and adolescents (<18 years) with BrS compared with controls, but this was not significantly associated with a high-risk phenotype.[336] Kakihara et al studied the LP after the pilsicainide provocation using Holter SAECG. The authors concluded that this resource may be useful for risk stratification of VF episodes in patients with BrS.[337] In patients with BrS, the body surface area of ST elevation and the presence of LPs correlate to the inducibility of VT during PVS and may be of value as a noninvasive marker for risk stratification in these patients.[338]

Positive ajmaline challenge

- ACM: Eventually positive Controversial. Ajmaline challenge in typical ACM characterizes a subgroup of elderly, predominantly female patients with the risk of developing dromotropic disturbances. Tachycardia-related events are rare. The indication of ICD implantation in recurrent syncope's is critical as the rate of lead-associated complications in a more than three years' follow-up is high.[339] Ajmaline challenge have been proposed to identify people at risk of SCD. However, its role is still controversial as it is

neither specific nor sensitive enough to guide further invasive investigations and managements. A type 1 pattern has also been induced in many cardiopathies, such as LQTS, ACM, HCM and myotonic dystrophy, without any clear arrhythmic risk profile. A positive ajmaline test does not provide any additional information on the risk stratification for MACE on asymptomatic individuals with a non-diagnostic Brugada ECG pattern.[340] Ajmaline challenge has several imperfections.[341] Tadros et al. from a single-center experience with 482 families commented: a positive ajmaline response was observed in a large proportion of UCA/ or SUD families. Their data emphasize the potential for confounding possibly false-positive ajmaline responses in this population, particularly at high doses, which could possibly lead to a misdiagnosis. Clinicians should consider all alternative causes in UCA/SUD and avoid ajmaline doses >1 mg/kg. A positive ajmaline challenge does not always mean you have BrS.[342, 343]

- **BrS:** Eventually positive.

BrS patients can show a left axis deviation (LAD) of the frontal QRS-axis during ajmaline challenge. The cause of this LAD is unclear. van der Ree et al aimed to determine (1) the prevalence of this left axis deviation and (2) to evaluate its cause, using the insights that could be derived from vectorcardiograms. Hence, from a large cohort of patients who underwent ajmaline provocation testing (*n* = 1430), the authors selected patients in whom a type-1 Brugada ECG pattern was evoked (*n* = 345). Depolarization and repolarization parameters were analyzed for

reconstructed VCGs and were compared between patients with and without a >30° LAD. The authors found: (1) that the prevalence of a LAD during ajmaline provocation testing was 18% and (2) that this LAD was not explained by terminal conduction slowing in the RVOT (4th QRS-loop quartile: +17 ± 14 ms versus +13 ± 15 ms, non-significant) but was associated with a more proximal conduction slowing (1st QRS-loop quartile). There was no important heterogeneity of the action potential morphology (no difference in the ventricular gradient), but a LAD did result in a discordant repolarization (spatial QRS-T angle: 122° versus 44°). Thus, although the development of the type-1 Brugada ECG pattern is characterized by a terminal conduction delay in the RVOT, BrS-patients with a LAD upon sodium channel blocker provocation have an additional proximal conduction slowing, which is associated with a subsequent discordant repolarization. Whether this has implications for risk stratification is still undetermined.[344]

Imaging techniques

- **ACM:** a) Classic right dominant form (ARVC/D): Regional wall motion abnormalities in RV Fat/LGE in RV myocardium. b) Left dominant form (LDAC and ALVC): Regional wall motion abnormalities in LV Non-compacted appearance LGE in the subepicardial and mid-wall LV myocardium.
- **BrS:** Normal or subtle abnormalities in CMRI. BrS patients with an SCN5A mutation have changes in RV volumes and function when compared with those without an SCN5A mutation. Mutation-positive patients have a higher likelihood of a spontaneous type 1 BrS-ECG,

which is associated with a higher incidence of events. CRMI may provide additional insight to distinguish between SCN5A mutation-positive and -negative BrS patients.[345]

Electrophysiological Study (EPS)

ACM:

Biopsy /Tissue characterization of wall

Infiltration of RV myocardium by fibrofatty replacement tissue, Localized RV aneurysm, Severe segmental dilation of the RV.

Major criteria: Residual myocytes<60% by morphometric analysis (<50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on EMB.

Major criteria: Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on EMB.

Minor criteria: Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on EMB. It is controversial due to patchy areas of myocardial involvement and limited sensitivity from sampling errors.[346]

EMB in ACM is characterized by epicardial substrate, endocardial hypertrophy, anterior and inferior wall involvement, peri tricuspid disease, LV laterobasal fat replacement.

BrS is associated with epicardial surface and interstitial fibrosis and reduced connexin-43 (Cx43) gap junction expression in the RVOT. This collocates to

abnormal potentials, and their ablation abolishes the BrS phenotype and life-threatening arrhythmias. BrS is also associated with increased collagen throughout the heart. Abnormal myocardial structure and abnormal late and fractionated potentials indicative of slowed conduction were identified are therefore responsible for BrS.[347] Despite an apparently normal heart at noninvasive evaluation, EMB detected structural alterations in all 18 patients with BrS. Mutations in the SCN5A gene, identified in 4 of the 18 patients, may have induced concealed structural abnormalities of myocardiocytes that accounted for paroxysmal arrhythmic events.[348] Coronel et al studied a BrS patient without clinically detected cardiac structural abnormalities underwent cardiac transplantation for intolerable storms with multiple ICD discharges. The patient's explanted heart was studied electrophysiologically and histopathologically. Whole-cell currents were measured in HEK293 cells expressing wild-type or mutated sodium channels from the patient. The RVOT endocardium showed activation slowing and was the origin of VF without a transmural repolarization gradient. Conduction restitution was abnormal in the RVOT but normal in the LV. RVH and fibrosis with epicardial fatty infiltration were present. HEK293 cells expressing a G1935S mutation in the gene encoding the cardiac sodium channel exhibited enhanced slow inactivation compared with wild-type channels. Computer simulations demonstrated that conduction slowing in the RVOT might have been the cause of the ECG changes.[349]

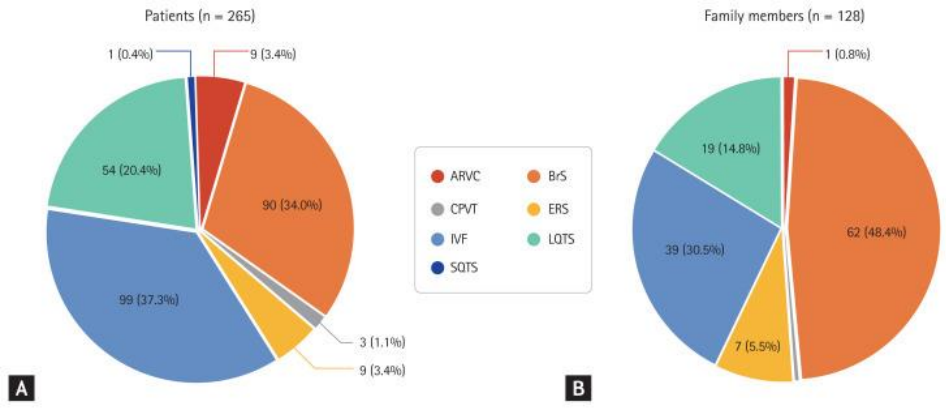
I) Natural history

- **ACM:** SCD, is the first manifestation of the disease in 11% to 22% of patients.[350] RV or biventricular CHF.

- **BrS:** Syncope, SCD, nocturnal agonal respirations, unexplained CA or documented VF/PVT at rest or during sleep,

II) Prevalence

- **ACM:** The estimated prevalence in the general population ranges from 1 in 1,000 to 1 in 5,000. Peters refers 1:1,000 to 1:1,250.[33]
- **BrS:** the prevalence of BrS, affect 5 in 10,000 people,[351] and its real impact on SCD is uncertain. The worldwide prevalence of BrS is about 0.05% and is more prevalent in Southeast Asia;[352] In the Asian population was estimated at 0.9%.[353] BrS is more prevalent in Southeast Asian ethnic groups and was considered a familial disease due to the presence of syncope and/or SCDs in several members of the same family, however, the genetic alteration was only noted in 1998.[354] The highest prevalence was reported in Southeast Asia (1.8 per 1,000); the lowest was found in North Africa (0 per 1,000). BrS in Asians was nine times more common than in Caucasians and 36 times more common than in Hispanics.[280] Oh, in the Korean population, registered the distribution of inherited arrhythmias in probands and their family members.[355] Figure x



Distribution of inherited arrhythmias in probands (A) and their family members (B) in the Korean population. ARVC, Arrhythmogenic Right Ventricular Cardiomyopathy; BrS, Brugada Syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; ERS, early repolarization syndrome; IVF, idiopathic ventricular fibrillation; LQTS, long QT syndrome; SQTS, short QT syndrome.

III) Gender, sex ratio and risk

- **ACM:** M/F 3:1[197] sex-based differences in the incidence are conflicting. Italian studies report that it is more common in males with an approximate ratio of 3:1,[37] on the other hand the United States and the Dutch ARVC/D cohorts report similar incidence between males and females.[3, 38]
- **BrS:** M/F 8:1. Female sex decreases risk.[282, 283] Sinus node dysfunction in females increased risk.[356]

IV) Predominant gene mutation

- **ACM:** Mutation in genes encoding any of the five major components of the cardiac desmosome—*PKP2* (encoding plakophilin2), *DSG2* (encoding desmoglein-2), *DSP* (encoding desmoplakin), *DSC2* (encoding desmocollin-2), and *JUP* (encoding junctional plakoglobin)—can result in ARVD/C. ≈50% of symptomatic individuals harbor a mutation in one of the five major components of the cardiac desmosome.[357]
- **BrS:** SCN5A. encoding the ion channel Nav1.5), which have been reported in > a 25% of all patients.

Very rarely also PKP2 The first iPSC-based model carrying a relatively infrequent mutation in PKP2 (c. 2484C>T) was identified by Cerrone et al. This mutation causes BrS symptoms and a reduced INa, deficit that can be restored in vitro at the cellular level via transfection of wild-type PKP2.[110] Penetrance of *PKP2* mutations was higher with increased age and male sex, with male mutation carriers more likely than female mutation carriers to have both structural and conduction abnormalities.[358]

V) Main complaints

- **ACM:** Palpitations, cardiogenic dizziness, syncope, and or UCLA/CA, progressive CHF.
- **BrS:** Syncope, UCA, high risk of SCD.[359] Agonal breathing.

VI) Events circumstances

- **ACM:** During or immediately after exercise: facilitated by catecholamine's. class I anti-arrhythmic agents eventually.
- **BrS:** At rest or during sleep enhanced by vagotony, fever, or β-adrenergic blockers, class I anti-arrhythmic agents. electrolyte disturbances, drugs, or medication, cocaine, anesthetics, antidepressants, and antihistaminic agents).

VII) ECG changes characteristic

- **ACM:** Fixed
- **BrS:** Dynamic

VIII) ECG depolarization /conduction dromotropic abnormalities/disturbances

- **ACM:** Right precordial QRS prolongation (>110 ms) of the QRS complex, Epsilon waves in the right precordial leads (Mayor criteria?) its identification and interpretation are influenced by ECG filtering and sampling rate, with large interobserver variability.[147] Consequently, Padua researches, consider epsilon waves in right precordial leads a minor ECG criterion, QRS delayed S wave upstroke with TAD ≥55 ms in the right precordial leads. Terminal activation duration (TAD) is measured from the nadir of the S wave to the end of all depolarization deflections and is prolonged if 55 ms in any of the V1–V3 leads in the absence of CRBBB.[319] Nasir et al. reported the delayed S wave upstroke defined from the nadir of the S wave up to the isoelectric line in $V_{1-3} \geq 55$ ms, as a sensitive criterion representing terminal activation delay[145] (**major criteria**).
- **BrS:** Prolonged QRS duration measured from lead II or lead V2 ≥120 ms,[322] QRS fragmentation. Presence of in at least four spikes in one or at least eight spikes in all of the precordial leads, increase risk[323] in QRS complex duration (>110º) in right precordial leads, in absence of CRBBB: parietal block,[183] coved and saddle-back types with day-to-day variation, right precordial high take-off, ST elevation followed by TWI ("coved-type morphology"), type 1 Brugada pattern. The type 1 is required for the diagnosis of BrS whereas the significance of saddle-back type ECG (type 2), which is inadequate for the diagnosis, has not been fully established. S wave >0.1 mV and/or >40 ms increased risk.[326] Type 1 Brugada pattern in the inferior leads increase risk;[327] Nasir et al reported the delayed S

wave upstroke defined from the nadir of the S wave up to the isoelectric line in $V_{1-3} \geq 55$ ms, as a sensitive criterion representing terminal activation delay[145] (major criteria).

IX) ECG: repolarization criteria

- **ACM:** Right precordial leads TWI leads V1–V3 or beyond, aged>14 years of age, without complete RBBB. Downsloping elevated ST-segment pattern in V_1 and V_2 occurs with more unipolar endocardial voltage abnormality, consistent with more advanced transmural disease.[304]
- **BrS:** characteristic repolarization pattern (type 1 Brugada ECG) and type 2. The last one is not diagnosis. Inferolateral early repolarization pattern. J wave > 0.1 mV in at least two inferolateral leads. Increased risk, with conflicting data.[305, 311] T-wave alternans. Post-exercise ST-segment elevation at the early recovery phase during exercise test. Increased risk, but needs to be confirmed.[310, 318] Prolonged T-peak—T-end interval.

VI) The most common ventricular arrhythmias

- **ACM: Major criteria:** NSVT or SMVT of LBBB morphology with superior axis (negative or indeterminate QRS in inferior leads, and positive in lead aVL). Frequent PVCs (1000/24h). **Minor criteria:** >500 PVCs per 24 h (Holter).
- **BrS:** Polymorphic VT, VF, PVC with short coupling. Phase 2 reentry (or ‘local re-excitation’) leading to fast polymorphic VT, may degenerate into VF. RVOT and conduction system delay, with progressive fibrosis on the conduction system.

VII) Late potentials (LPs) on the signal-averaged ECG (SAECG)

- **ACM:** Late potentials by SAECG in ≥of 3 parameters in the absence of a QRS duration >110 ms on the standard ECG Filtered QRS duration >114 ms Duration of terminal QRS. Root mean square voltage of terminal 40 ms ≤20 mV Terminal activation duration of QRS ≥55 ms measured from the nadir of the S-wave to the end of the QRS, including R', in V1, V2, or V3, in the absence of complete RBBB. Note: LPs on SAECG are no longer included among the Padua criteria, since the use of SAECG technique has been abandoned by most centers because of its non -specific findings and limited diagnostic accuracy.[146]
- **BrS:** SA-ECG could be helpful to identify high-risk patients for its high negative predictive value as the first step.[325]

XIII) Positive ajmaline test

- **ACM:** Eventually positive (controversial).[339, 340, 343]
- **BrS:** Eventually positive

XIV) Imaging techniques

- **ACM:** RV morphofunctional changes: global dilatation, bulgings/aneurysms, and wall motion abnormalities.
- **BrS:** have no signs of overt SHD detectable.

XV) EPS

- **ACM:** EPSs are not included in the diagnostic criteria, but may be important for differential diagnosis including RVOT tachycardia. Further differential diagnoses include sarcoidosis, congenital

abnormalities, myocarditis, pulmonary hypertension, DCM, and athletic cardiac adaptation, which may mimic ACM.[360]

- VF occurrence. Increased risk, with conflicting data, particularly with three extra stimuli.[277, 312, 361]

XVI) Biopsy/Tissue characterization of wall

a) ACM: The role of EMB in ACM is controversial as there is a concern for perforation of the already thinned out RV wall. Some experts believe that non-invasive testing may be utilized, while others think that a fibrofatty replacement of myocardium on cardiac biopsy may provide certainty to the diagnosis. A reasonable approach is to employ non-invasive tests as the first-line option, considering EMB for cases of diagnostic uncertainty. Broadly, EMB can be used to diagnose CHF of unknown etiology, cardiac sarcoidosis, amyloidosis, inflammatory cardiomyopathies, storage diseases, cardiac masses, in diagnosing cardiac tumors except for typical myxomas (as they have the potential to embolize from manipulation), and antineoplastic side effects (suspected anthracycline cardiomyopathy). It can also be used in the surveillance of patients with a heart transplant or to differentiate between constrictive pericarditis and RCM or RV myocarditis and ACM. Analysis of conventional EMB using such biomarkers could improve diagnostic sensitivity and accuracy but widespread clinical application of this approach requires further validation. Although the pathological demonstration of myocardial degeneration and fibrofatty replacement is regarded as the

diagnostic “gold standard”, endomyocardial biopsy has not been consistently helpful in recognizing the disease partly owing to its patchy nature and lack of histological abnormalities at early stages. Recently, novel molecular markers, such as anti-DSG2 antibodies are a sensitive and specific biomarker for ACM,[116] have been identified that could prove useful if adopted in clinical practice, but further research is required to confirm their diagnostic usefulness.[362]

b) **BrS:** The vast majority of BrS patients have a macroscopic absence of SHD, although several studies have described the presence of sub-clinical or minor SHD.[363] Further, genetic and immunohistological analyses of 6 forensic samples from BrS family members revealed tissue- and molecular-level changes, specifically, an increase in epicardial collagen and fibrosis and a decrease in gap junction Connexin43 expression, especially in the RVOT.[347] Despite these reports, the role of fibrosis in BrS is uncertain, and the clinical phenotype concomitant with cardiac fibrosis remains a matter of ongoing scientific investigation, although a strong association has been shown in some genetic studies.[364, 365]

Typical ECG of ACM

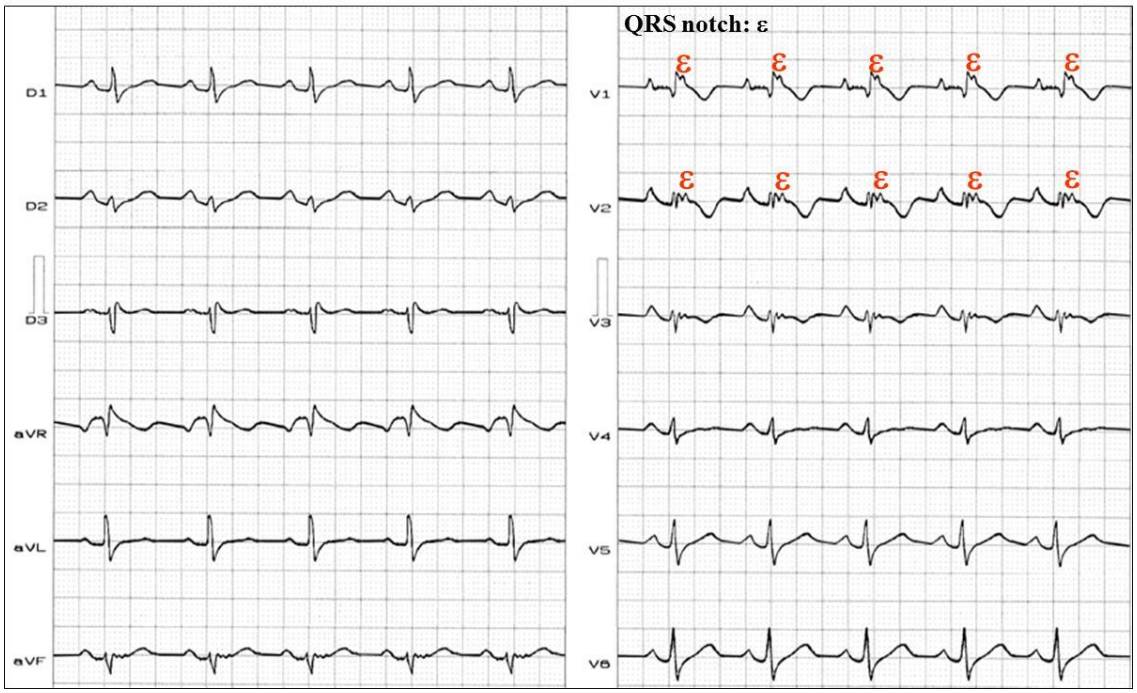


Figure 75. Sinus rhythm, CRBBB, terminal notch located in the J point (epsilon wave). The epsilon wave could be the result of delayed activation in the RV. It is visible from V1 to V3 and in the frontal plane leads. T wave inversion is observed in V1 to V3, characteristic of ACM.

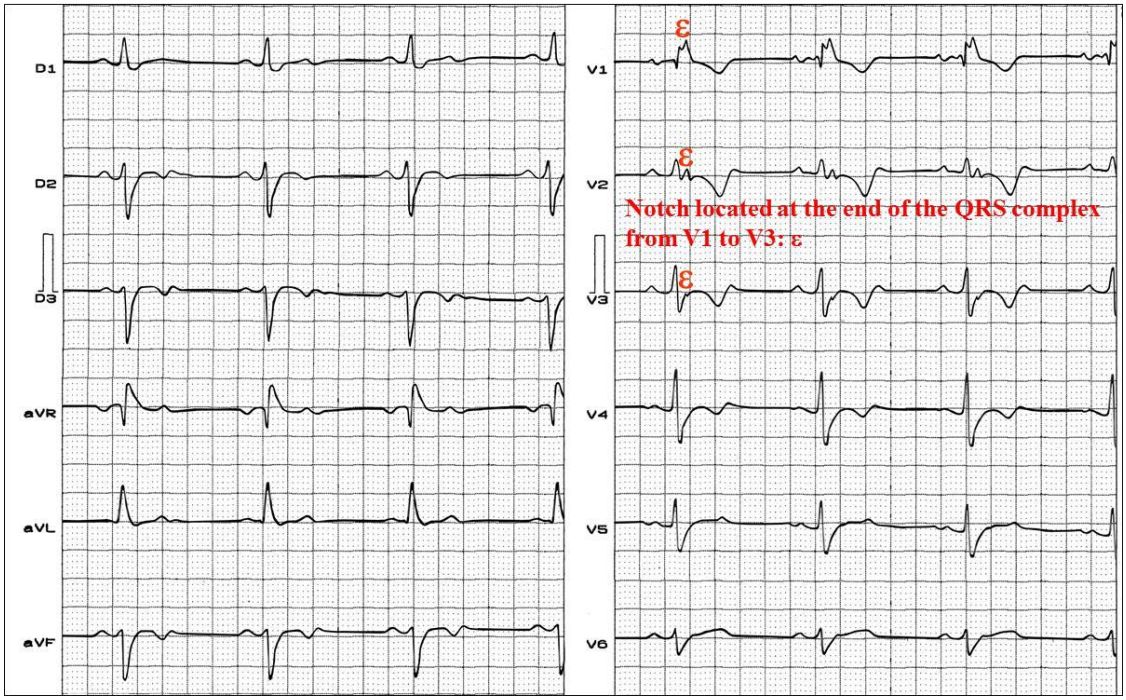


Figure 76. Sinus rhythm, HF: 44 bpm, sinus bradycardia, PR interval: 175 ms, SÂQRS: -85º, QRSd: 185 ms, SIII > SII, LAFB, atypical CRBBB (qR pattern), notch located near the J point (epsilon wave) visible from V1 to V3, characteristic of ACM. Negative T wave from V1 to V4.

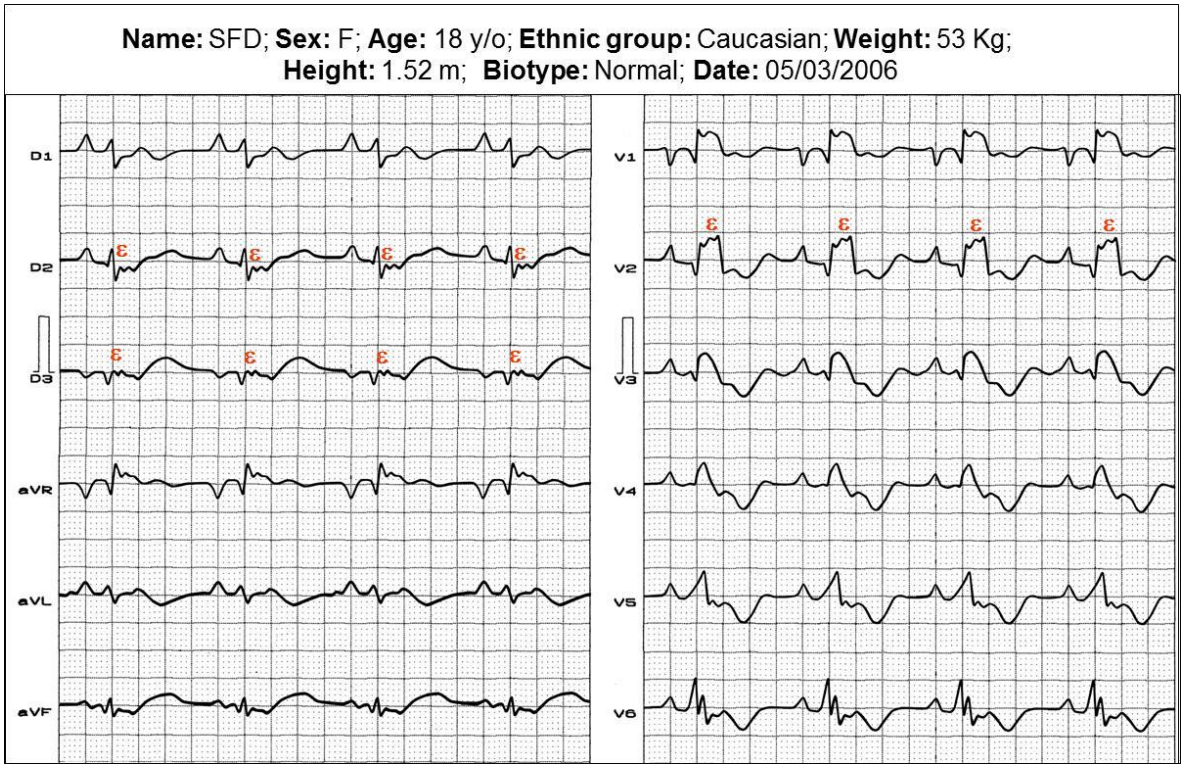


Figure 77. Clinical diagnosis: Arrhythmogenic Right Ventricular Dysplasia. Severe right CHF. ECG diagnosis: sinus rhythm, HR: 60 bpm; P wave: SAQRS near 0º, voltage: 3 mm, duration: 130 ms; negative polarity in V1 and positive in V2, q wave in V1 and V2: biatrial enlargement? Or right ventricular mega enlargement? QRSd: 230 ms (CRBBB); epsilon waves are observed in numerous leads.

ECG/VCG correlation in the frontal and horizontal planes

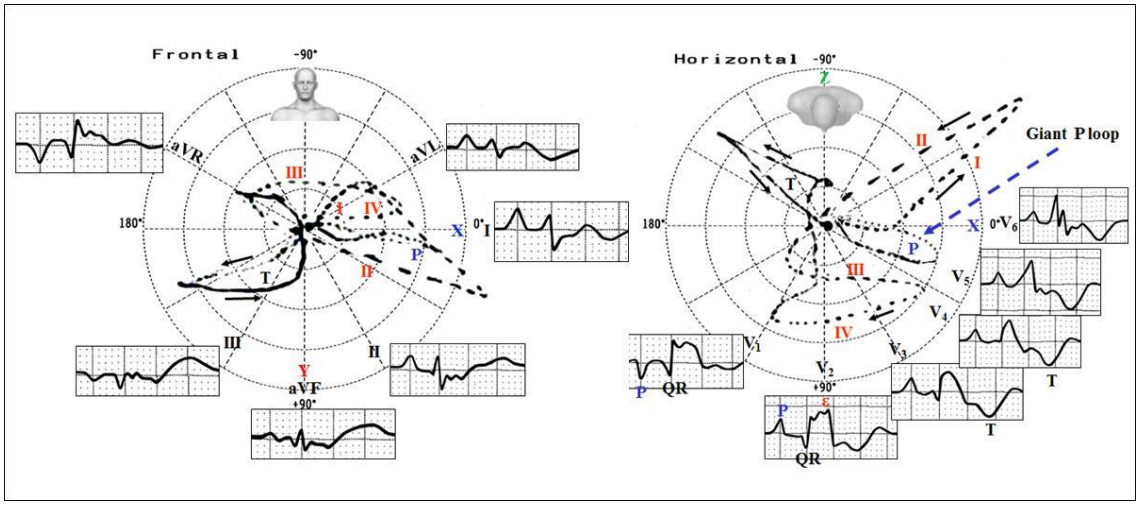


Figure 78. Late forces appendix located in anterior quadrants, biatrial enlargement.

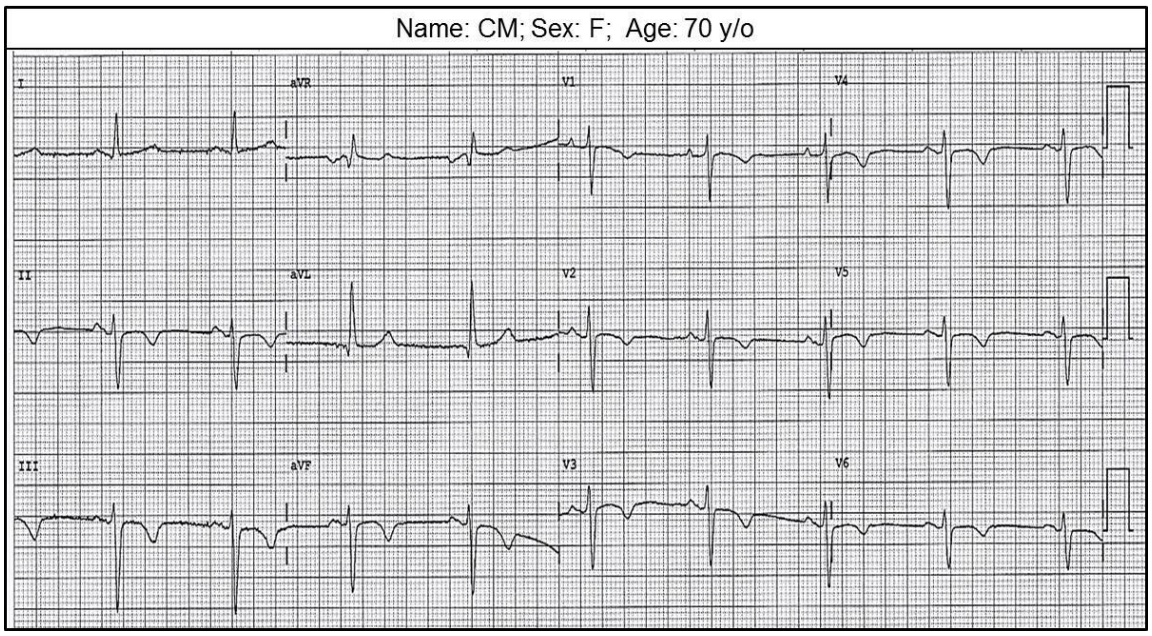


Figure 79. Clinical diagnosis: No family history. NSVT. ARVD (histology, RV angio) + LV involvement. Arrhythmias well controlled with propaphenon + atenololol. ECG diagnosis: Sinus rhythm, HR 55bpm, QT 456 ms/QTc 437 ms.

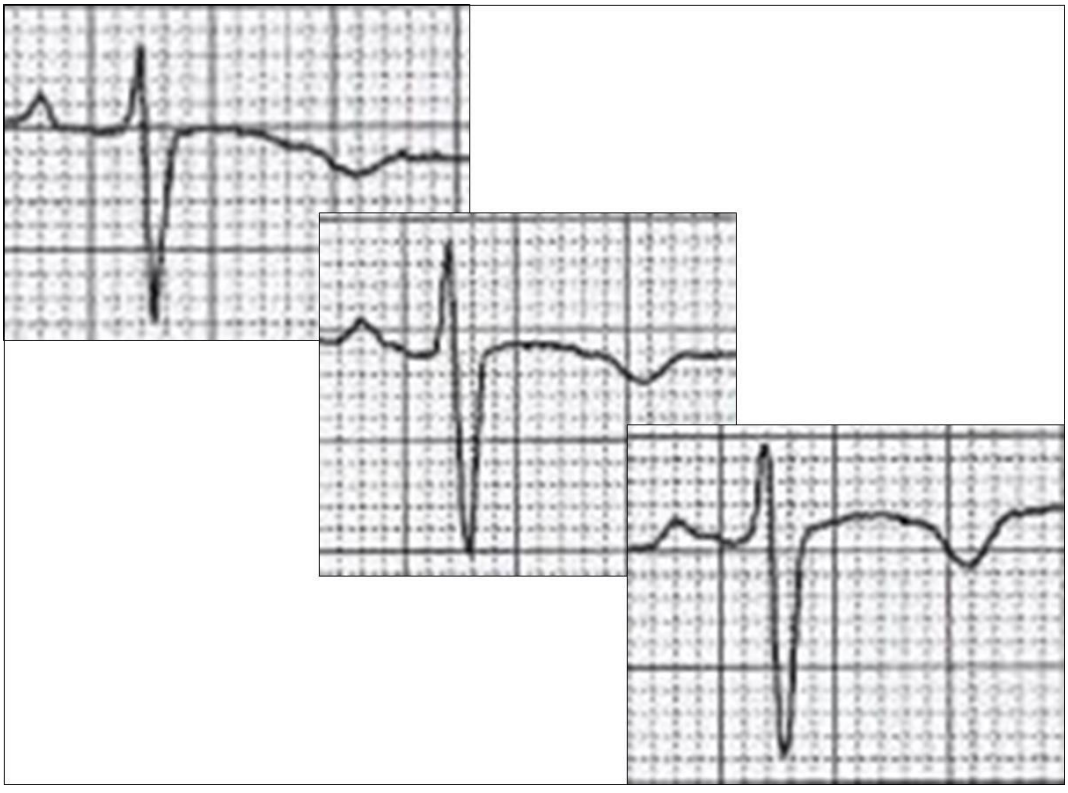


Figure 80. ECG.

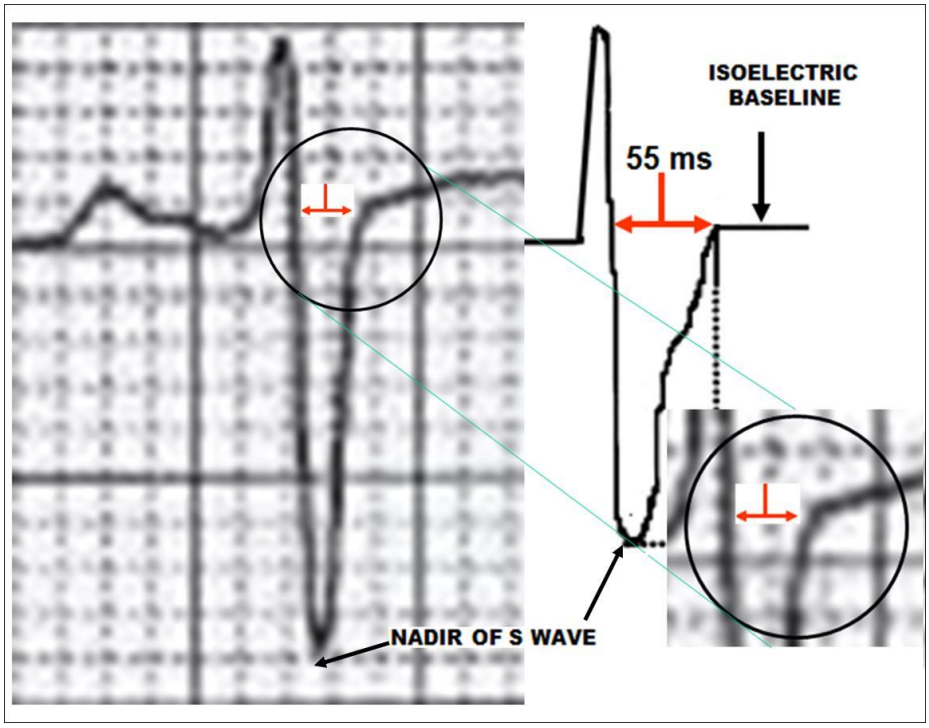


Figure 81. ECG.

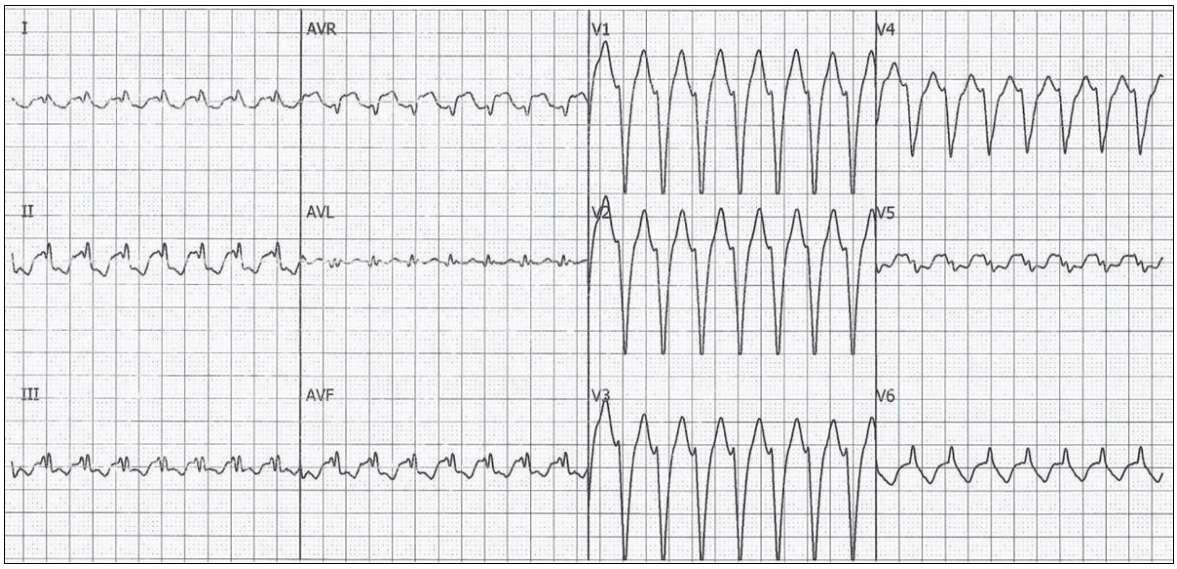


Figure 82. First syncope. ECG at E.R. Therapy: DC shock. QRSd = 141 ms; HR = 182 bpm. During sustained monomorphic VT from the RVOT.

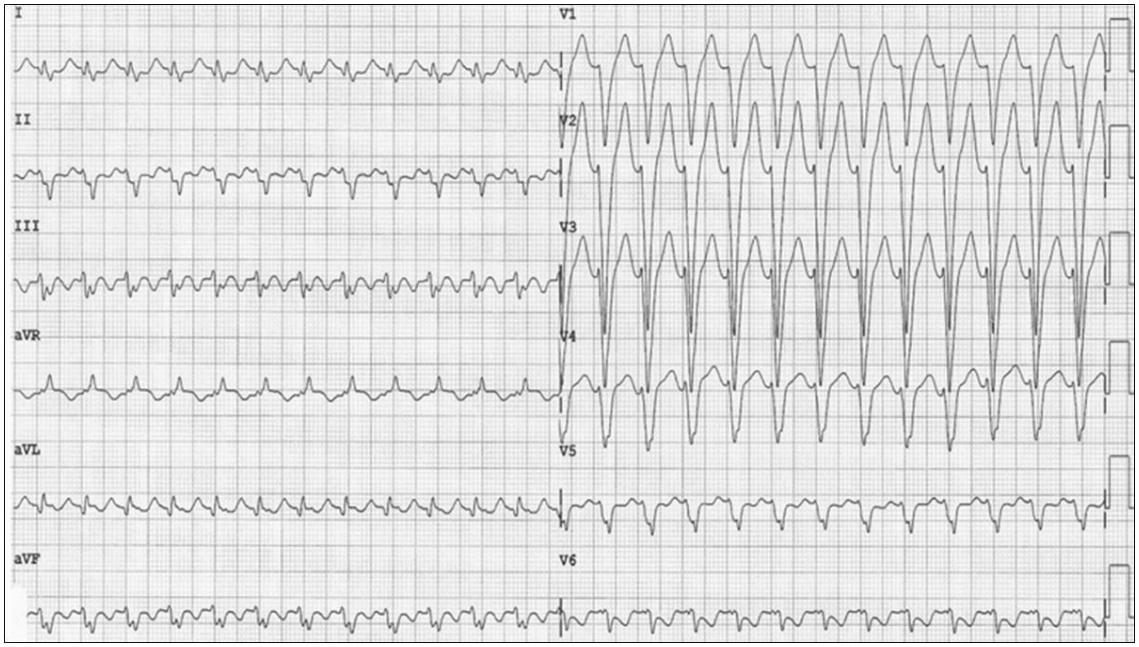


Figure 83. Second syncope at emergency Therapy: DC shock. Home therapy: Propafenone + atenolol.

J.P.S. F, 28 years old.

2007: She was admitted with syncope and SMVT, with morphology of LBBB (see next slide).

Diagnosis of Ebstein's anomaly in Sept 10, 2008

Pre-operative echo: dilated RV with low setting of the septal fascicle of the tricuspid valve with severe tricuspid insufficiency. Surgical description: there is no

anatomical evidence of Ebstein's anomaly; severe tricuspid insufficiency with significant RV dilatation.

24/07/12 Transtoracic ECHO →

EF: 63% ;

Right cardiac chambers with significant increase and presence of spontaneous contrast;

Preserved global and segmentary contractility of the LV;

RV systolic dysfunction;

Tricuspid bioprosthesis of normal aspect, presenting opening area by PHT of 2.1 cm^2 and mean gradient of 2.1 mmHg;

sPAP = 23 m

25/07/2012 Holter→rare PVCs.

Evolution: EPS: 10/08/2012: Ablation of cavotricuspid isthmus with bidirectional block. Protocol of ventricular pacing with induction of SMVT → Degeneration into polymorphic VT with hemodynamic instability → ECV (200 J); after flutter ablation, she presented sinus bradycardia (HR = 40 bpm), which soon improved (HR = 50 bpm) Implantation of ICD.

Tricuspid valve replacement was carried out, with bioprosthesis in December 2012

2012: SMVT + atrial flutter.

November 2014: Admitted with predominantly right CHF (jugular vein stasis, peripheral edema, ascites, but with clean lungs) ECHO shows: Significant RV and LV dysfunction (LVEF = 32%) and dysfunction of bioprosthesis with severe tricuspid insufficiency.

In my opinion, the diagnosis is in fact, arrhythmogenic right ventricular cardiomyopathy/ dysplasia. Fontaine leads made currently, reveal more prominent epsilon waves. Besides, high resolution ECG is positive. We are waiting for the full hemodynamic study. Probably a transplant will be made, depending on pulmonary resistance.

What do you think of this case?

2007

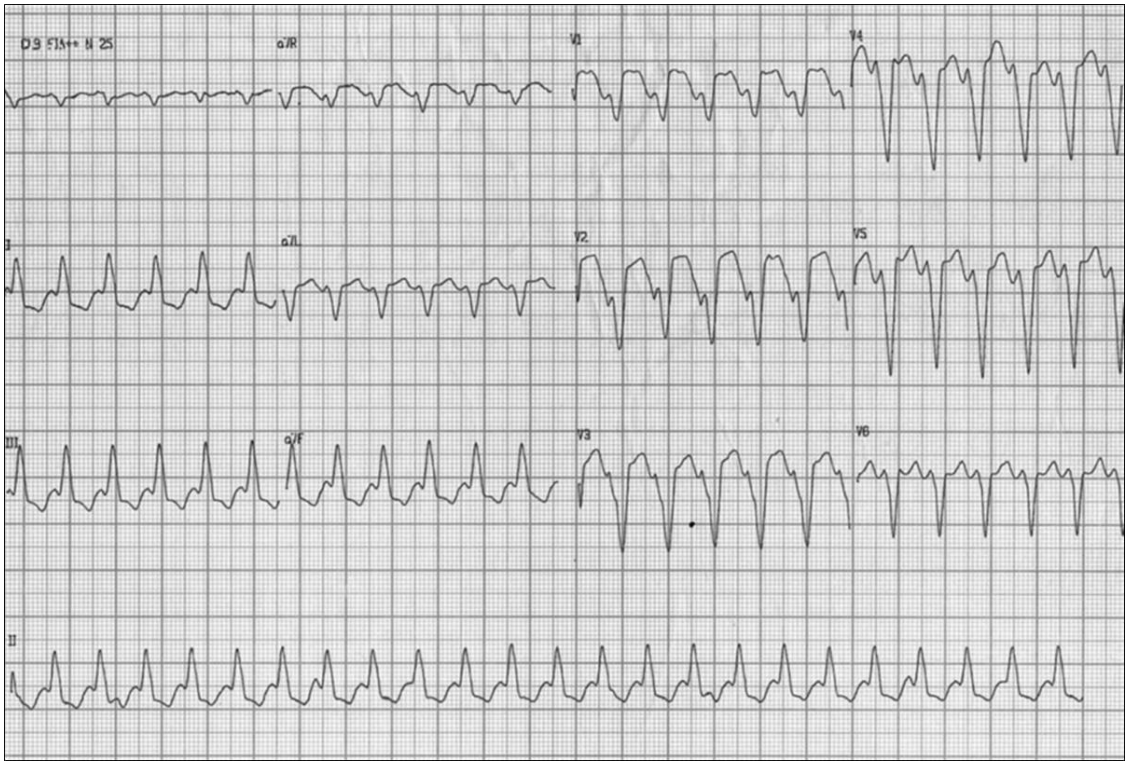


Figure 84. ECG.

2012

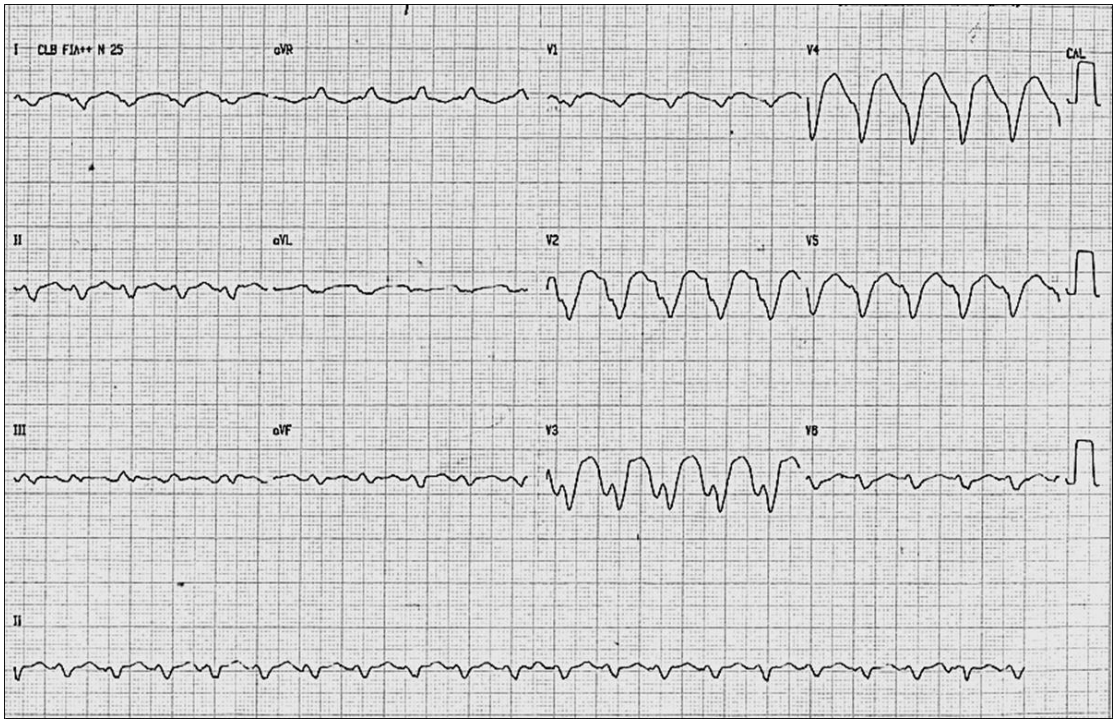


Figure 85. ECG.

22-08-2012

2N

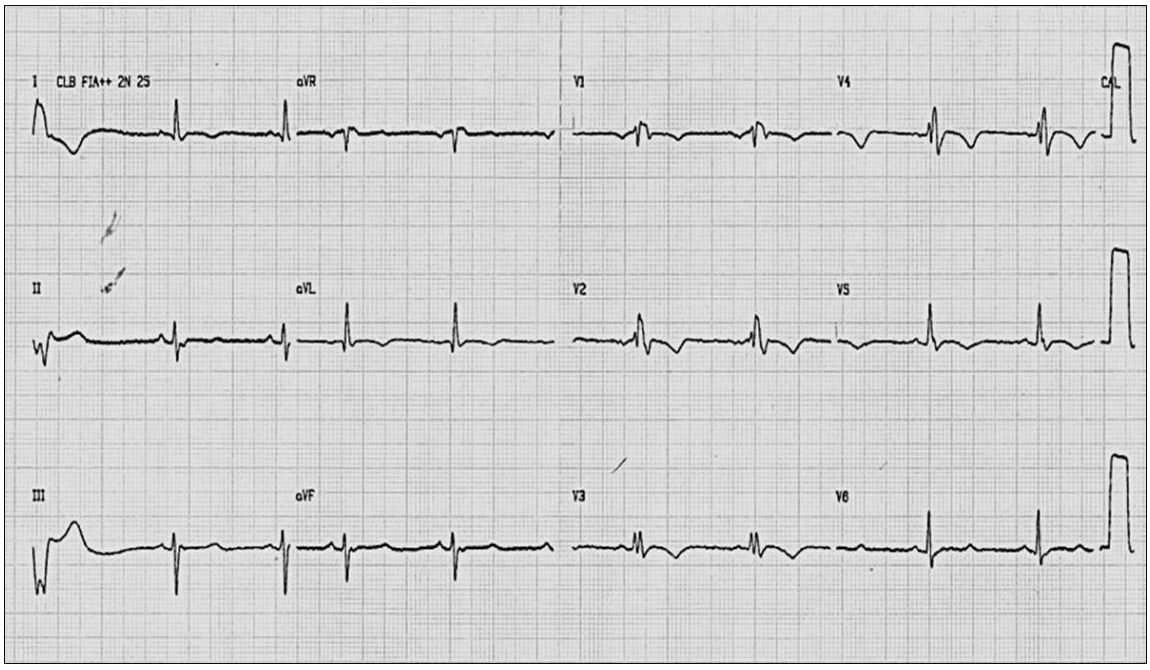


Figure 86. ECG.

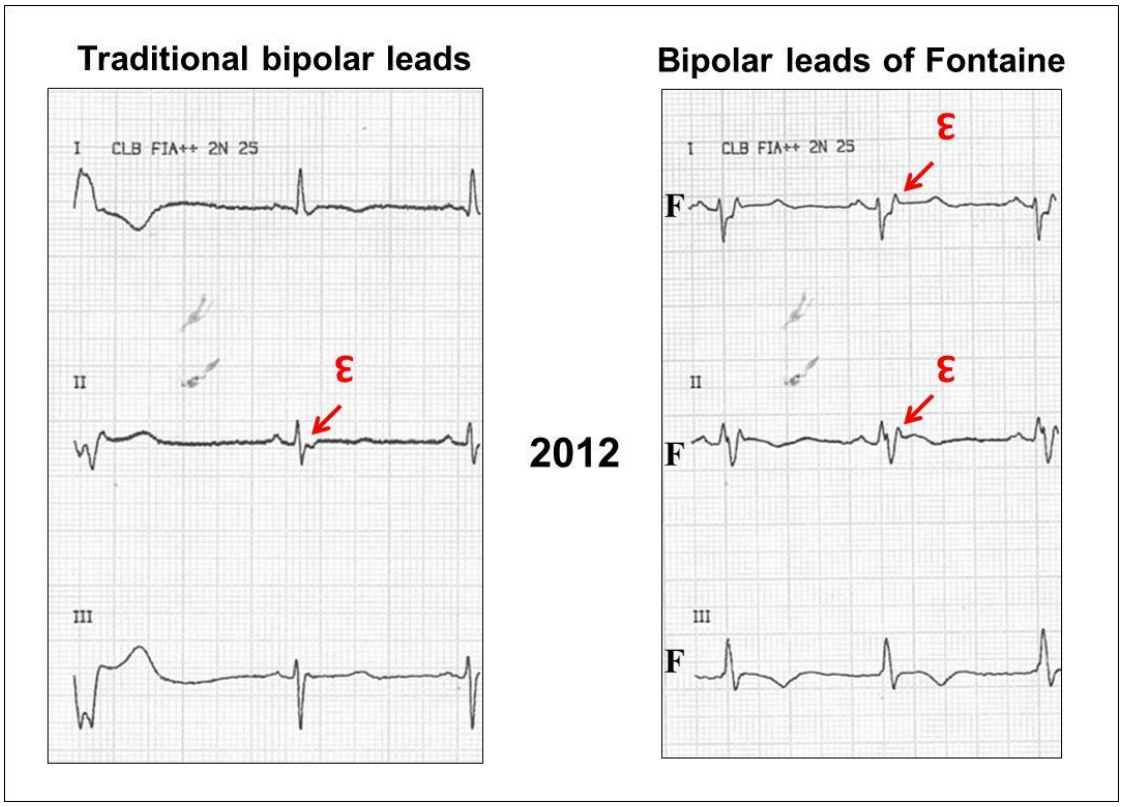


Figure 87. ECG.

ECG, November 2014

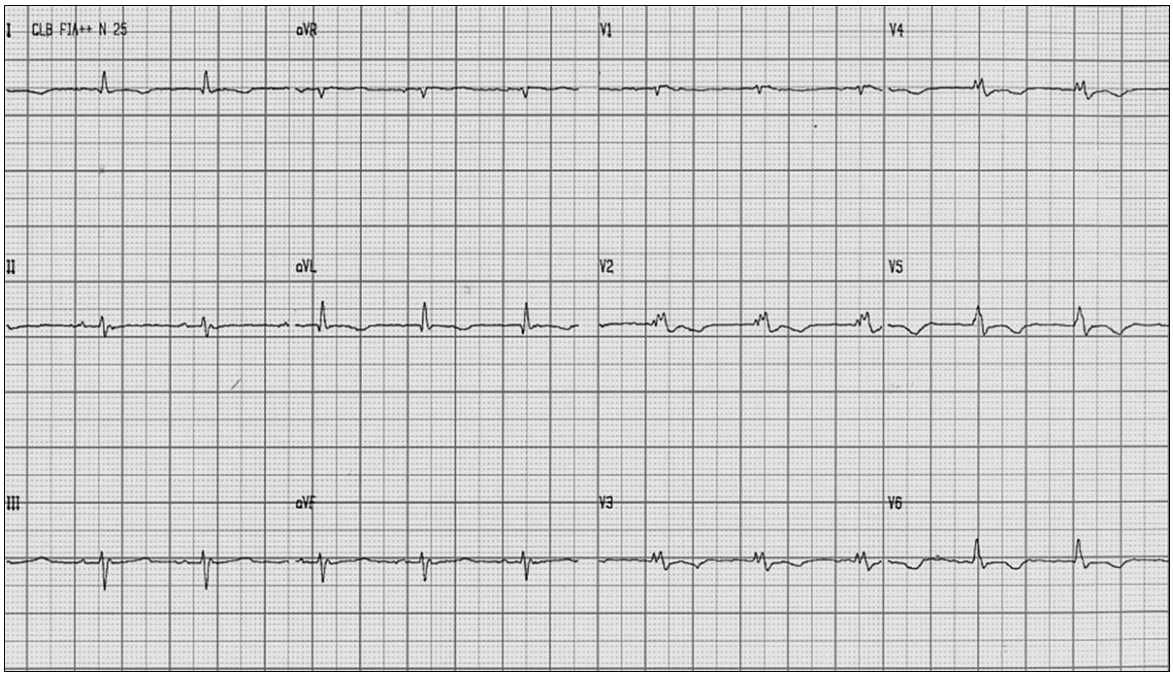


Figure 88. ECG.

2014

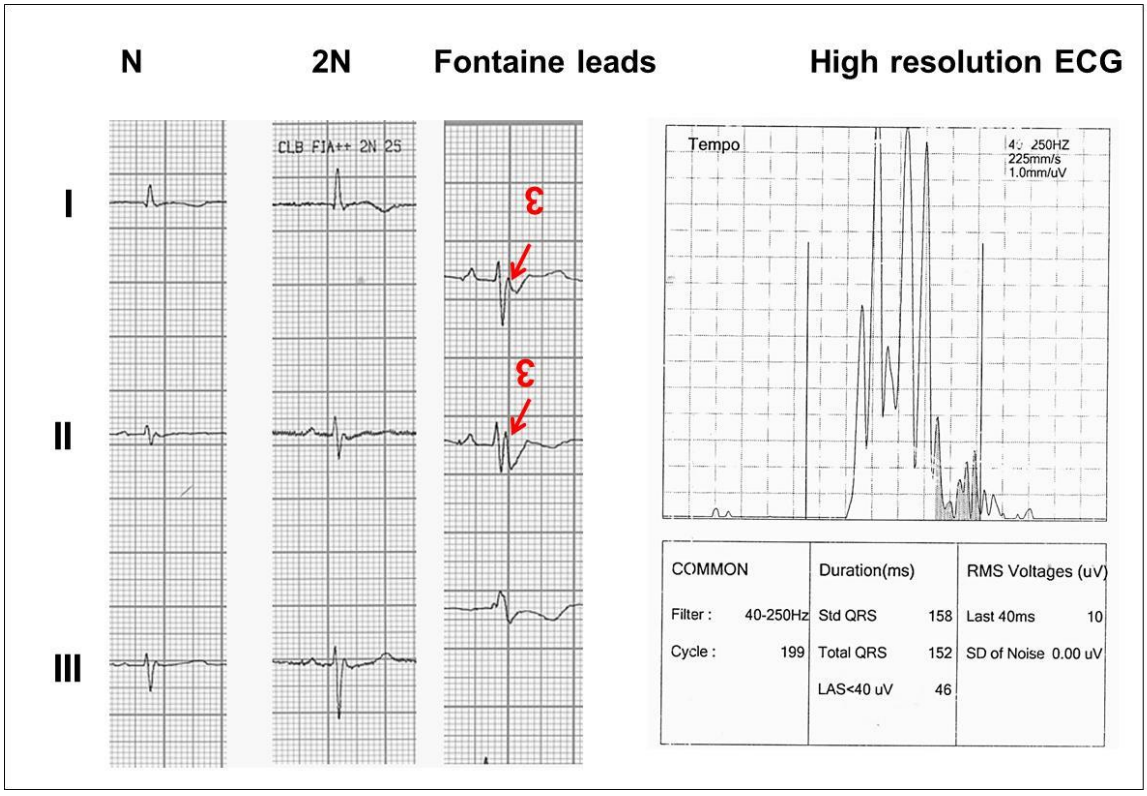


Figure 89. ECG.

Relationship between the site of origin and QRS complex configuration in VT

MVT that originates in the RV

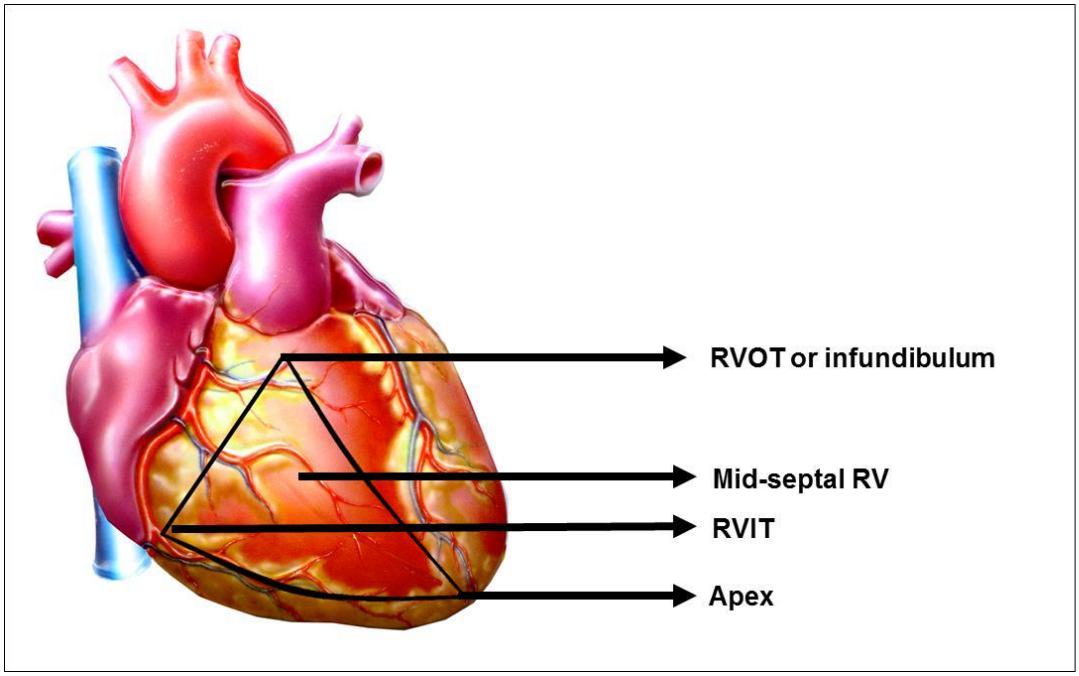


Figure 89. Figure.

Characteristic of MVT that originates in the RVOT (infundibulum)

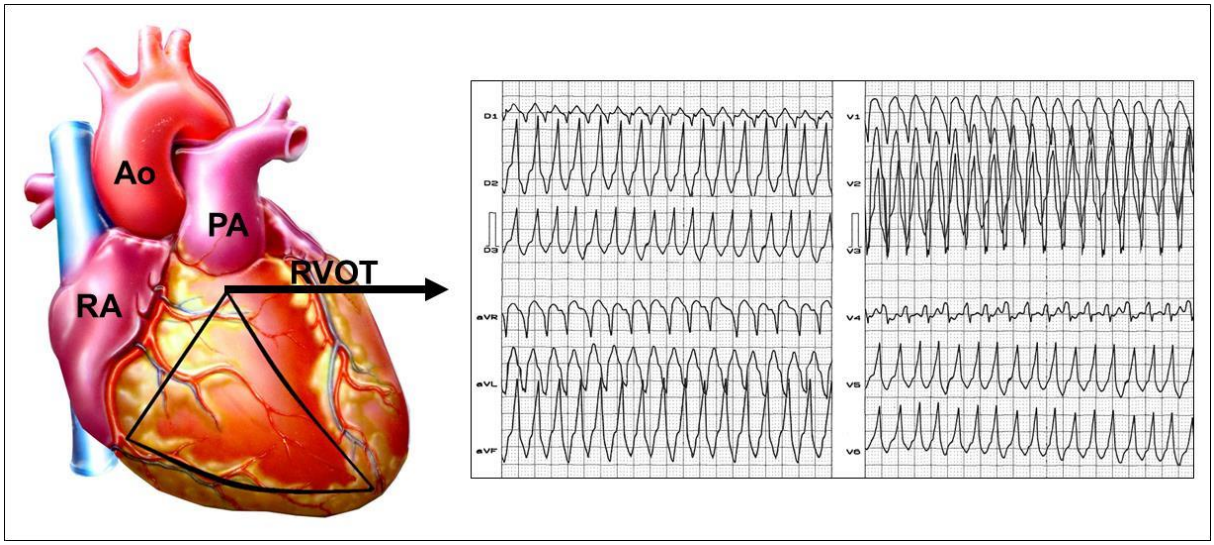


Figure 90. SMVT with CRBBB pattern and inferior axis in the frontal plane: positive complexes in inferior leads and negative in aVL and aVR. In this case, SÂQRS is located at the right of +90º, thus indicating origin in the RVOT. In these cases, SÂQRS is between +90º and +120º ("QS" type QRS in I).

MVT that originates in the RVOT (infundibulum)

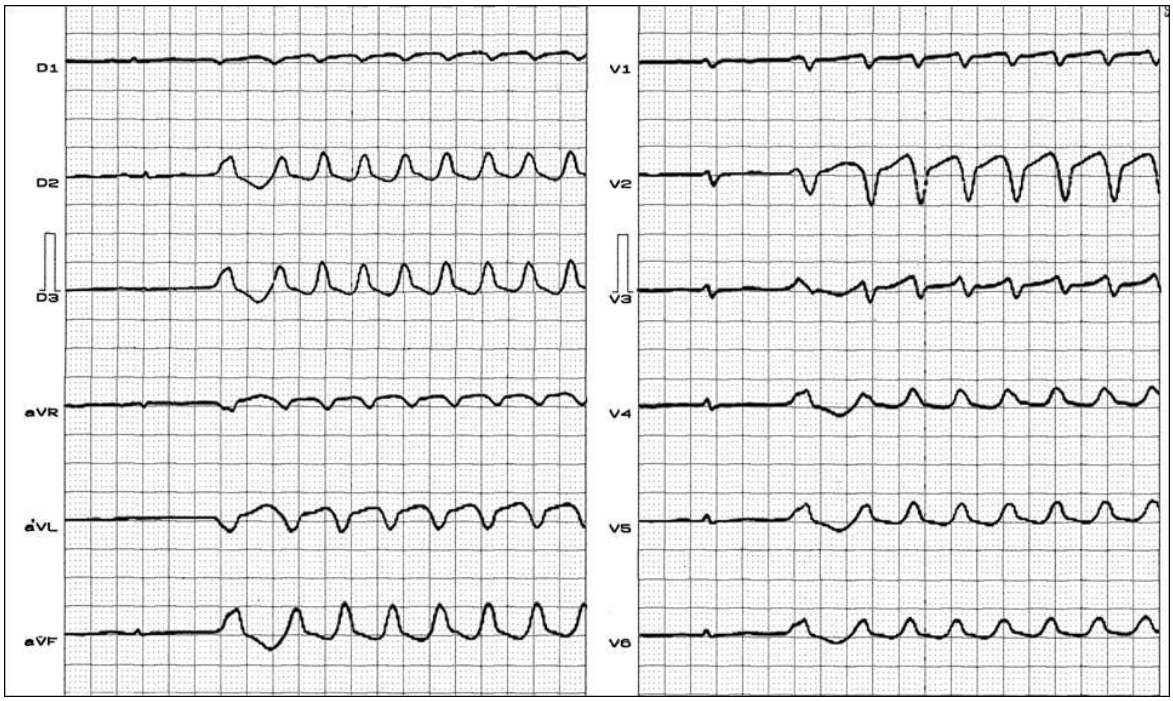


Figure 91. MVT that originates in the RVOT with CLBBB pattern and inferior axis in patient carrier of ACM after cardiac arrest.

MVT that originates in the RVIT

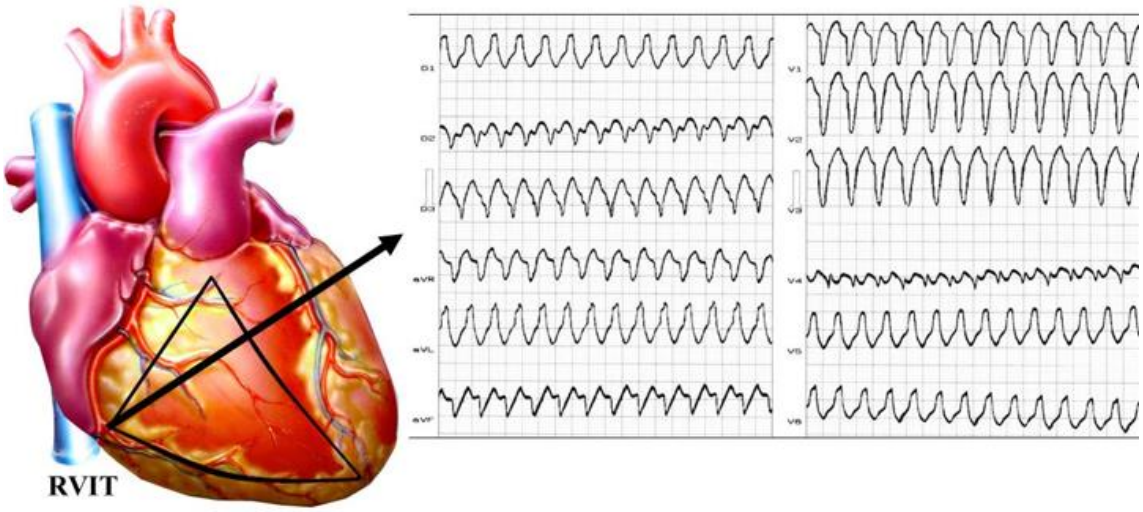


Figure 92. MVT with a heart rate of 214 bpm, pattern of CLBBB and electrical axis with extreme shift to the left: it originates in the RVIT. This VT with superior axis indicates presence of SHD.

MVT that originates in the right ventricle apex

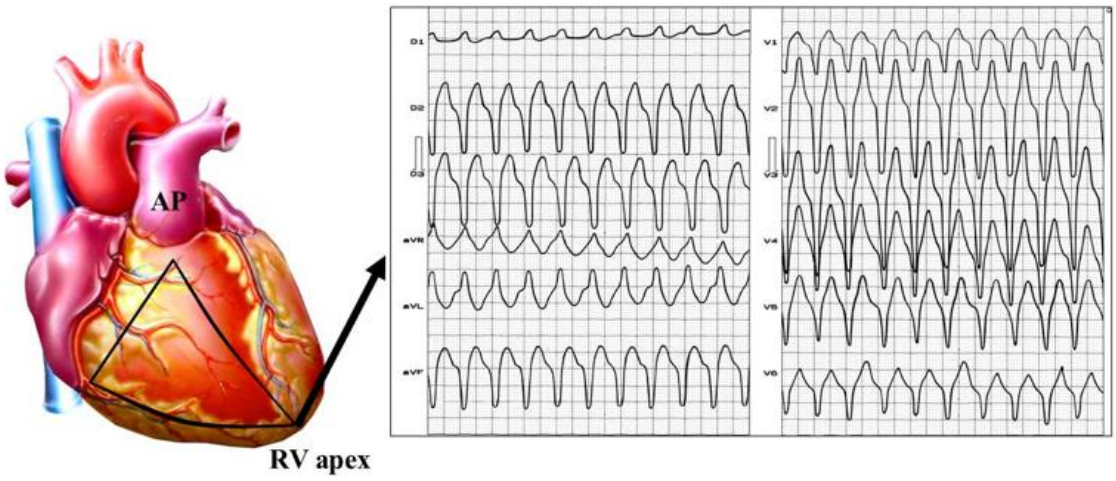


Figure 93. VT with CLBBB morphology and SÂQRS axis with extreme shift to the left: negative QRS complexes in inferior leads, positive in I, aVL and aVR, associated to negative QRS complexes from V1 to V4 or V1 to V6, which indicate focus of origin in the RV apex (it indicates SHD).

Value of vectorcardiogram in ACM

In 1988, researchers from Padua (Italy) showed vectorcardiographic tracings characterized by what is known today as RECD, by the superior fascicle of the right branch, in a series of 6 patients, 5 of which had ACM as it was shown, and one of them was attributed to IVF [366].

Tracings of this kind were interpreted as early repolarization [366].

In ARVD, in 18% of cases, pattern of IRBBB or ECD is observed and in approximately 15% of the cases, CRBBB.

In this entity, there is evidence of RB fascicular block, which occurs in the RV free wall, after the trunk of the left branch splits at the tip of the RV, at the base of the papillary muscle of the tricuspid valve.

The mechanism responds to dysplastic involvement of the free wall, in the so-called Dysplasia Triangle, the angles of which are formed by the RVOT, RVIT and the apex [180].

Its characteristic is the presence of ECD by the right branch, by one of the fascicles, known as selective, peripheral, parietal, monofascicular RBBB or ECD. This disorder is vectorcardiographically characterized by:

- Initial 10 to 20 ms vector heading predominantly forward and rightward (in normal conditions, this vector in 85% of the cases is heading forward and rightward) [367];
- QRS loop displays rapid passage from left to right between 40 and 60 ms in both planes (FP and HP);
- Possible extreme shift of SAQRS in the FP located between -30° and -90°;
- QRS loop with significant RECD (≥ 30 ms of very close dashes) after 60 ms, visible at least in 2 planes.
- When there is ST segment elevation, we verify that the onset of QRS loop (0 point) does not match the end of it (J point) . The J point is located ahead and to the right from the 0 point.
- QRS loop duration > 60 dashes or 120 ms: CRBBB;
- T loop in the HP located in the posterior quadrants. The more severe the RV involvement, the more backward and rightward the T loop.

Right branch fascicles of the right bundle branch in the RV free wall

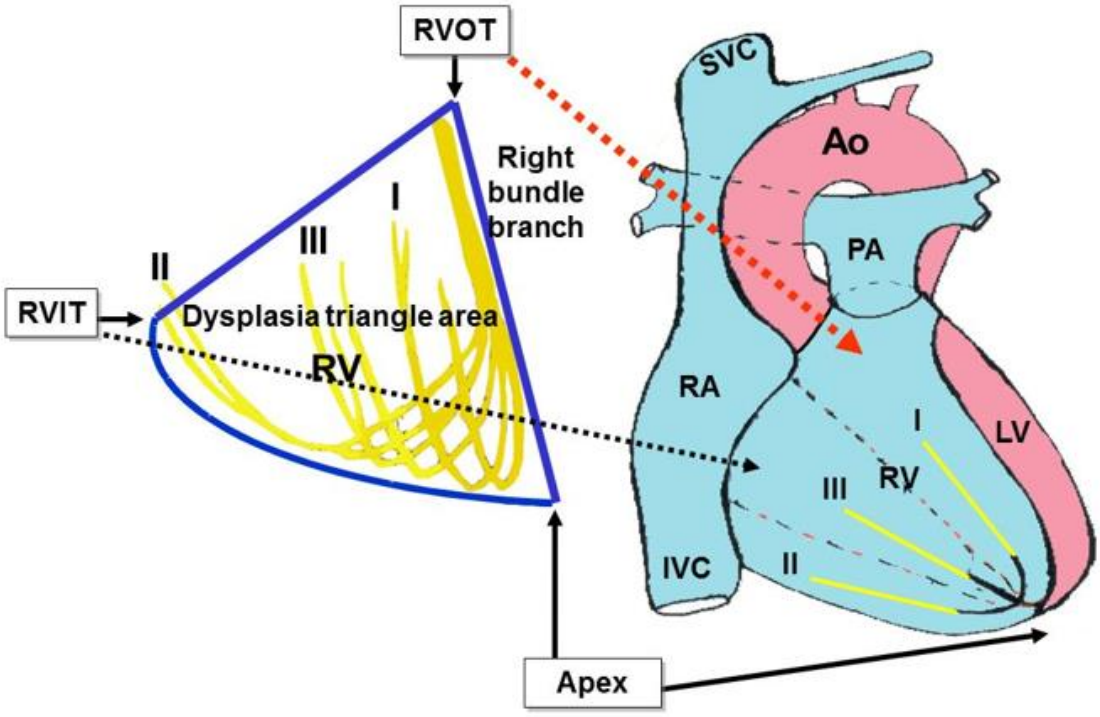


Figure 94. Right branch fascicles of the right bundle branch in the RV free wall.

VCG/ECG correlation of right precordial leads in ACM – FP and HP

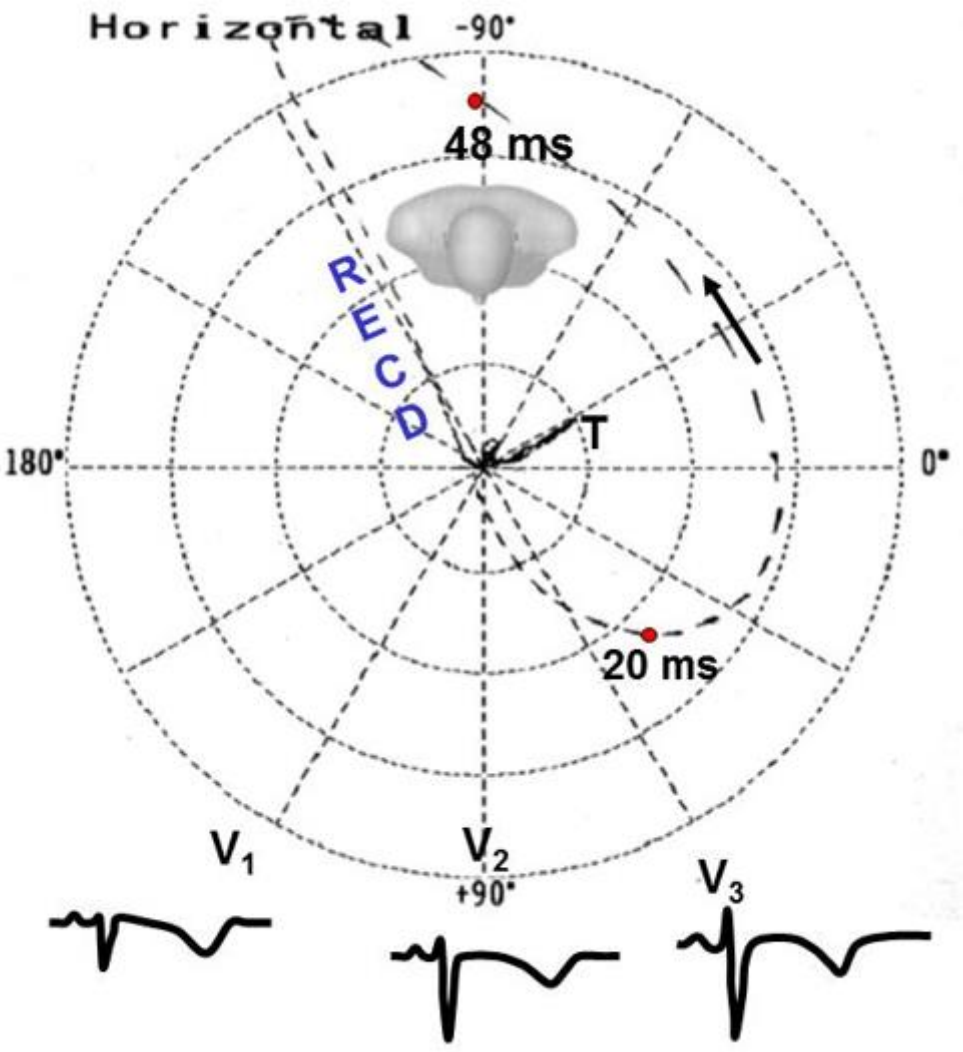


Figure 95. Initial 10 to 20 ms vector heading predominantly forward and leftward (in normal conditions this vector in 85% of cases is heading forward and rightward). Rapid passage from left to right at 48 ms. T loop located in the left posterior quadrant. Consequently, negative T waves are registered from V1 to V3.

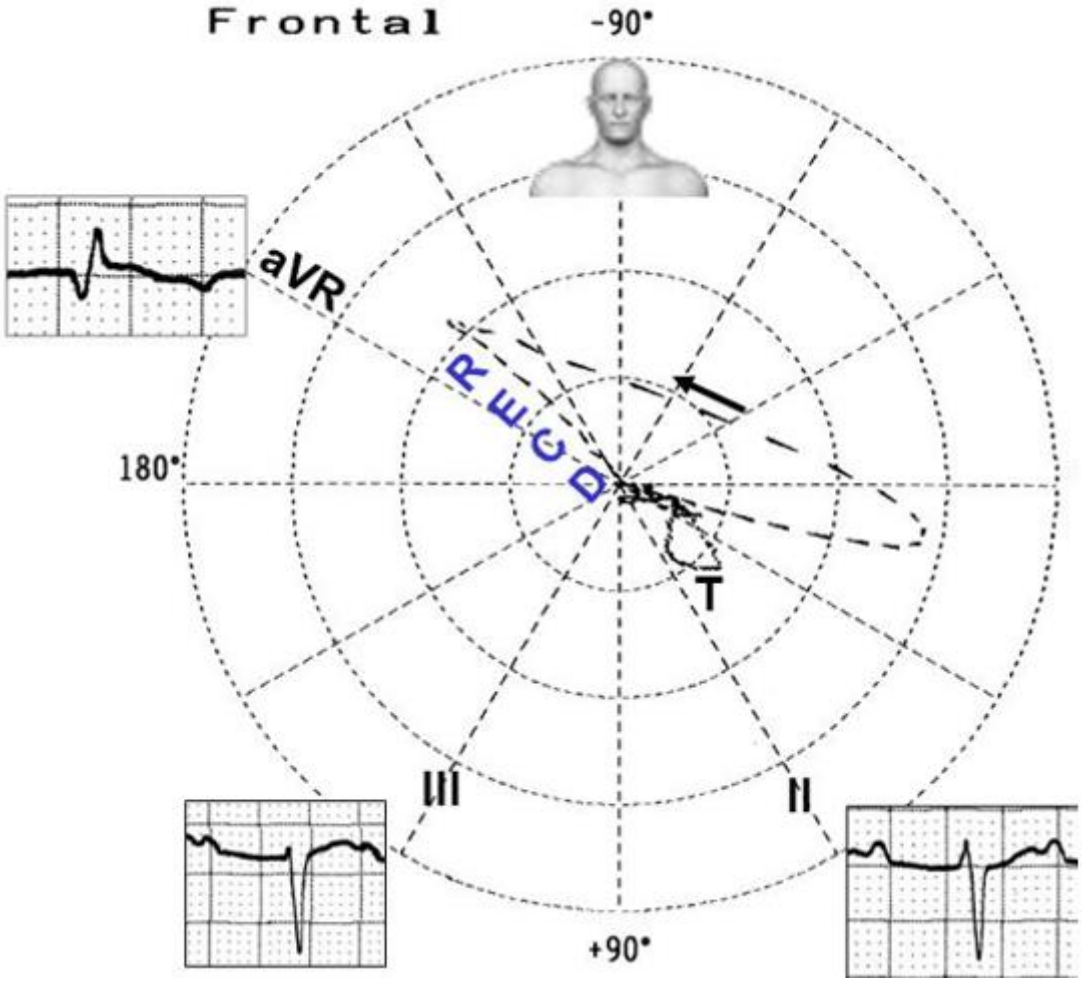


Figure 96. QRS axis located between -30° and -90° with RECD located in the right superior quadrant. SII > SIII in most cases (element of great significance for differential diagnosis with LAFB). As the RECD is in the right superior quadrant, there is prominent R wave in aVR.

36-year-old patient, episode of VF

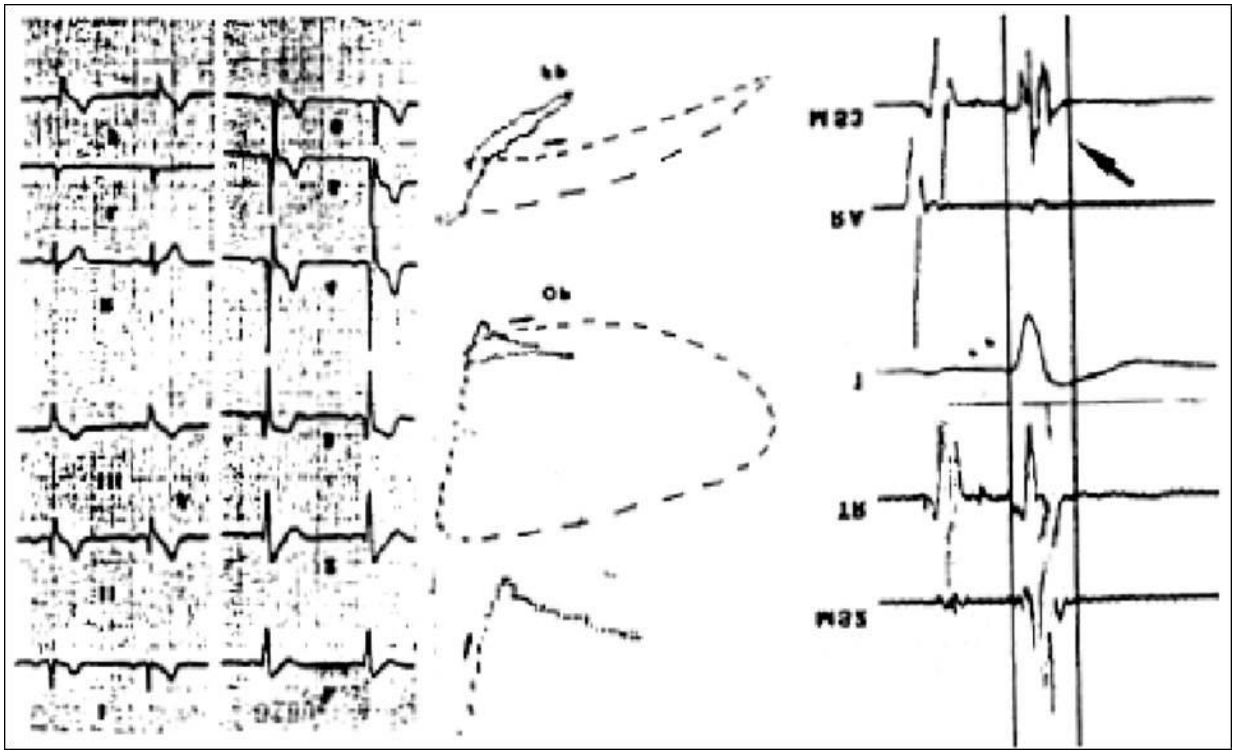


Figure 97. The authors interpreted this tracing as early repolarization pattern. Today we know that this is the typical type 1 ECG Brugada pattern, which from the vectorcardiographic point of view is diagnosed as RECD by one of the RB fascicles of the RBB [366].

ECG/VCG correlation in the frontal plane, Dr. Nava's patient

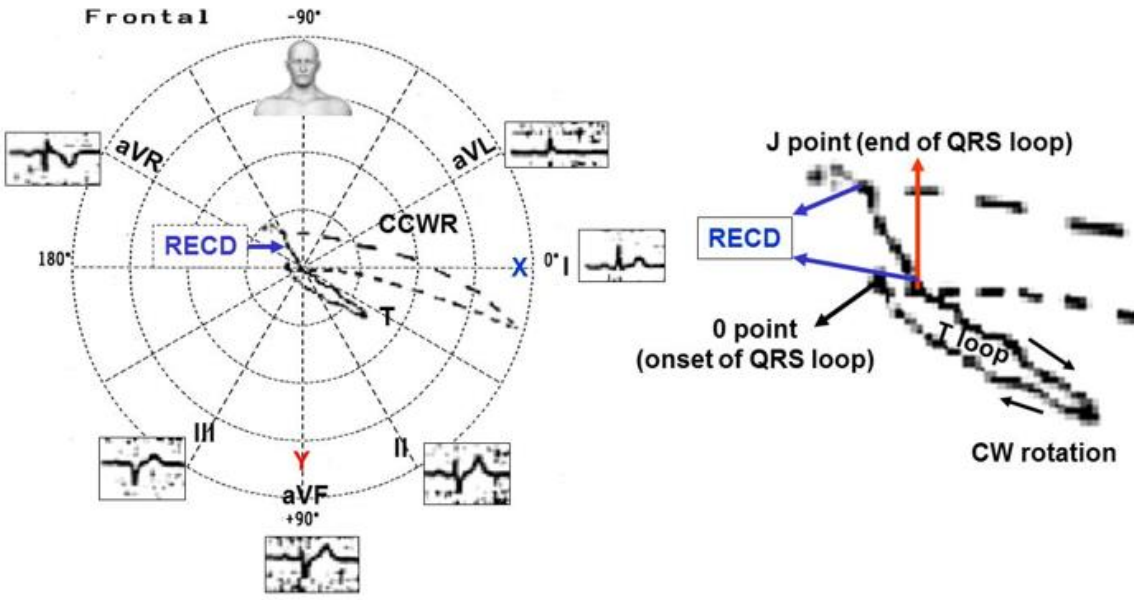


Figure 98. SÂQRS with extreme shift in left superior quadrant between -30° and -90°. Initial 10 to 20 ms vector heading below and to the left, rapid passage from left to right between 50 to 60 ms. The 0 point (onset of QRS loop) does not match J point (end of QRS loop). Both points move away in a proportional way to the degree of ST segment shift. Conclusion: RECD on right superior quadrant by the superior fascicle of the right branch, located in the RVOT.

ECG/VCG correlation in the horizontal plane, Dr. Nava's patient

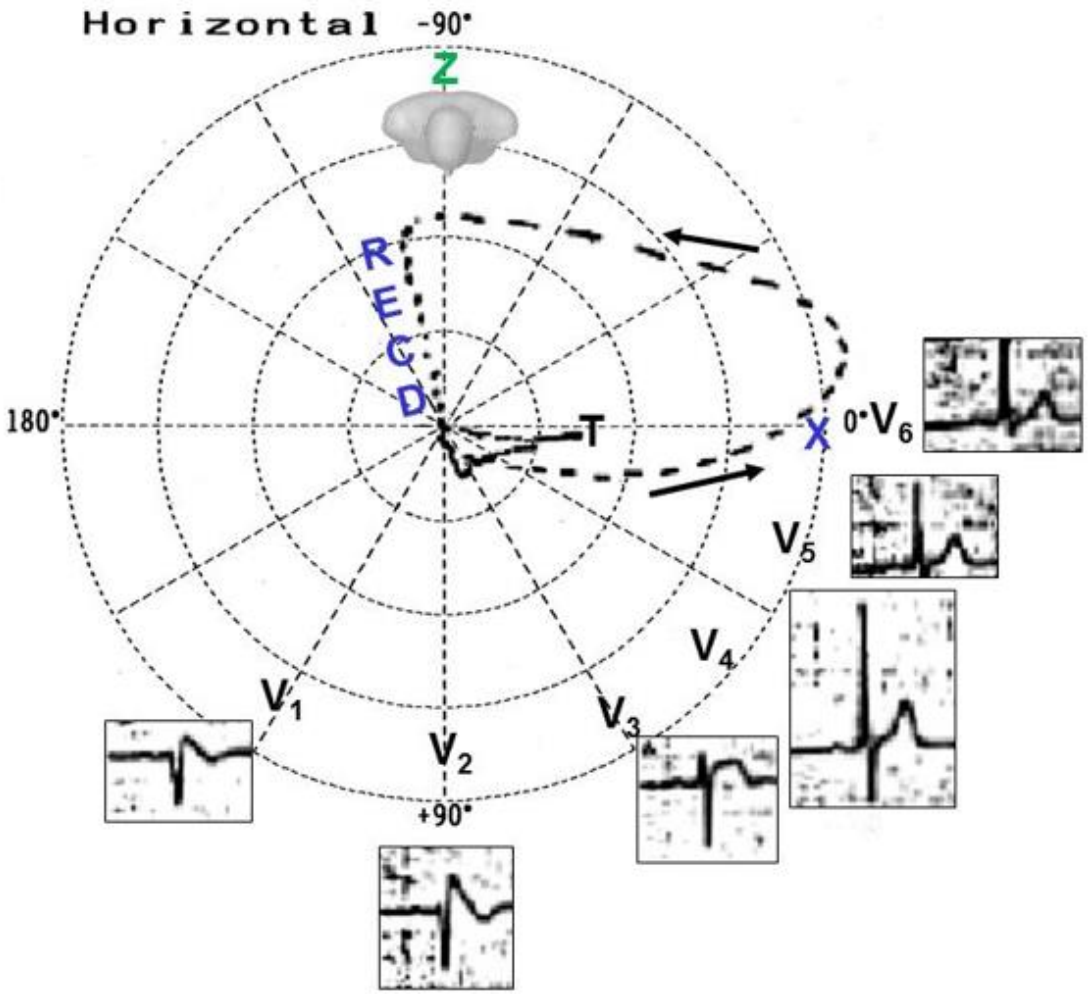


Figure 99. Initial 10 to 20 ms vector heading forward and leftward (typical RBBB), CCW rotation and RECD located in the right posterior quadrant. Conclusion: RECD with typical type 1 ECG Brugada pattern in the right precordial leads.

10 to 20 ms vector heading leftward and forward: typical of RBBBs (Luna Filho, Bocanegra et al. 1989)

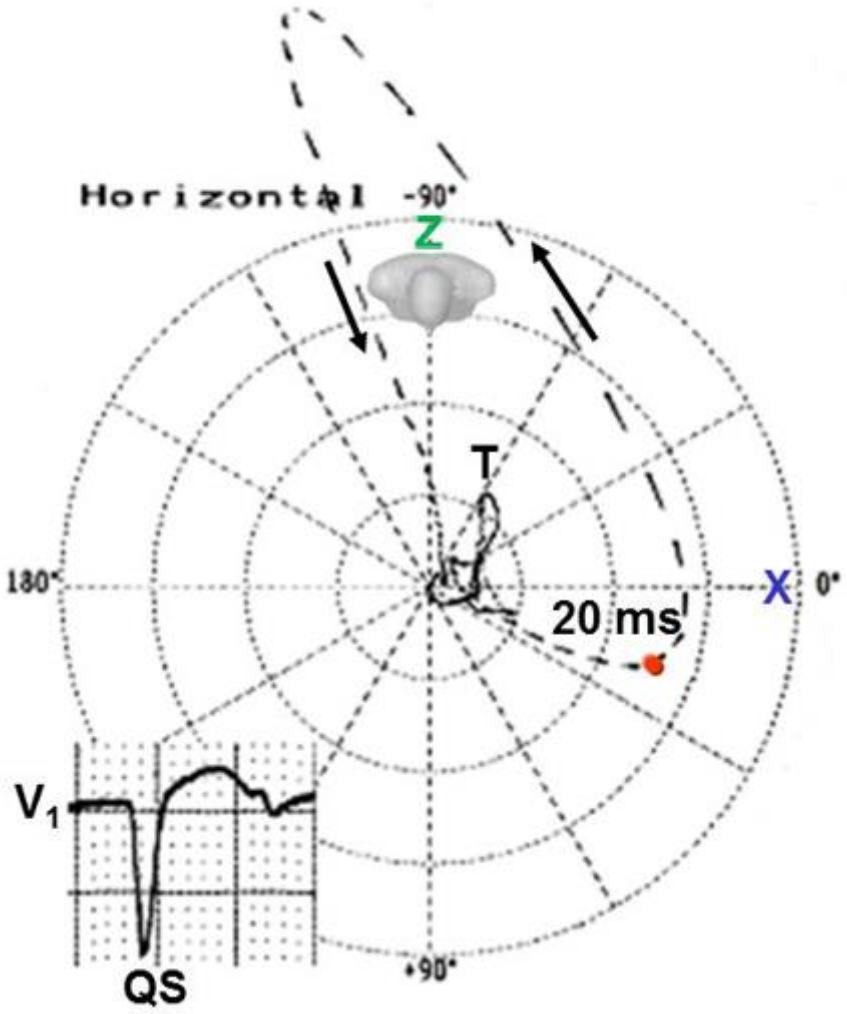


Figure 100. QRS loop in the HP with significant forces located in the right posterior quadrant, resembling type C RVH, 20 ms vector located in the negative hemifield of V1: QS pattern.

Male, 56 years old; Date 16/03/2002

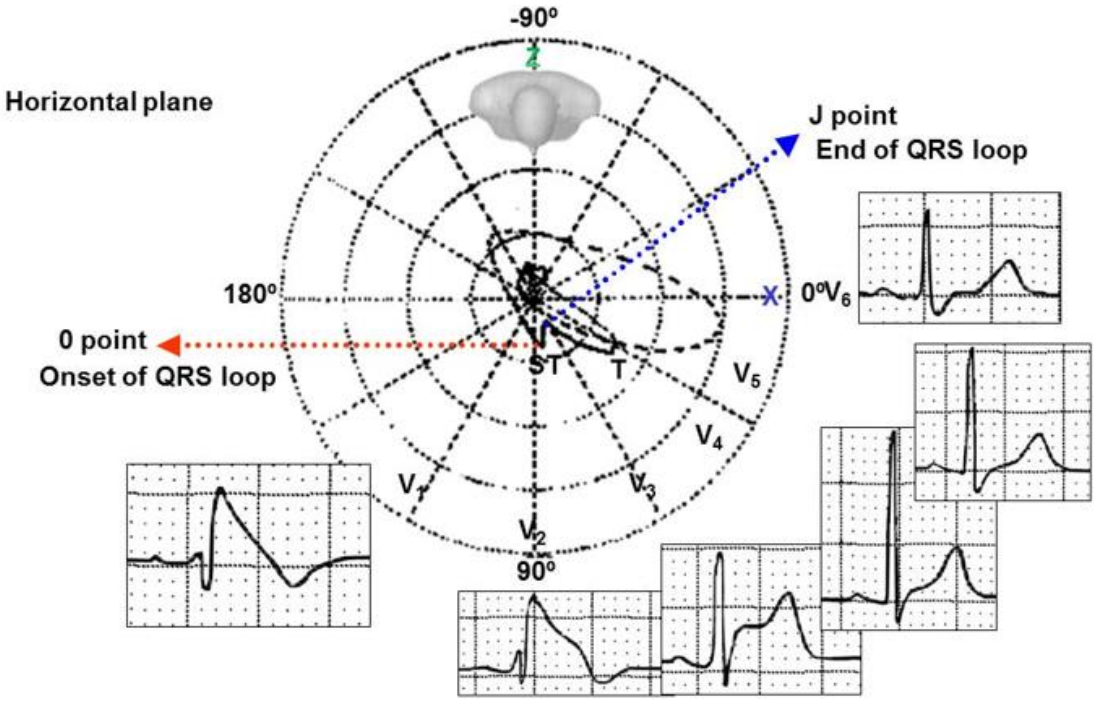


Figure 101. The onset of QRS loop (0 point) does not match its end (J point), which indicates significant degree of ST segment elevation.

T loop behavior in ACM and its relationship with RV end diastolic volume

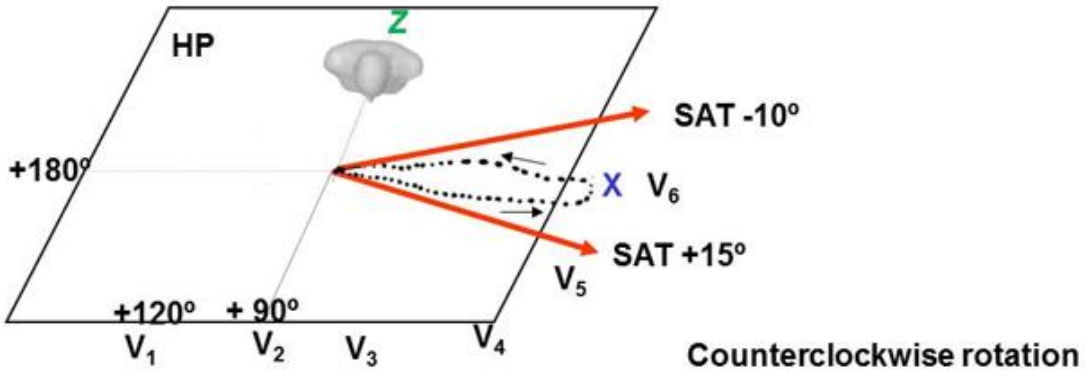


Figure 102. When the RV end diastolic volume is not very increased (in average 100 ml/m2). The T loop presents counterclockwise rotation in the HP and axis between +15º and –10º (average +5º).

T loop behavior in ARVD and its relationship with RV end diastolic volume

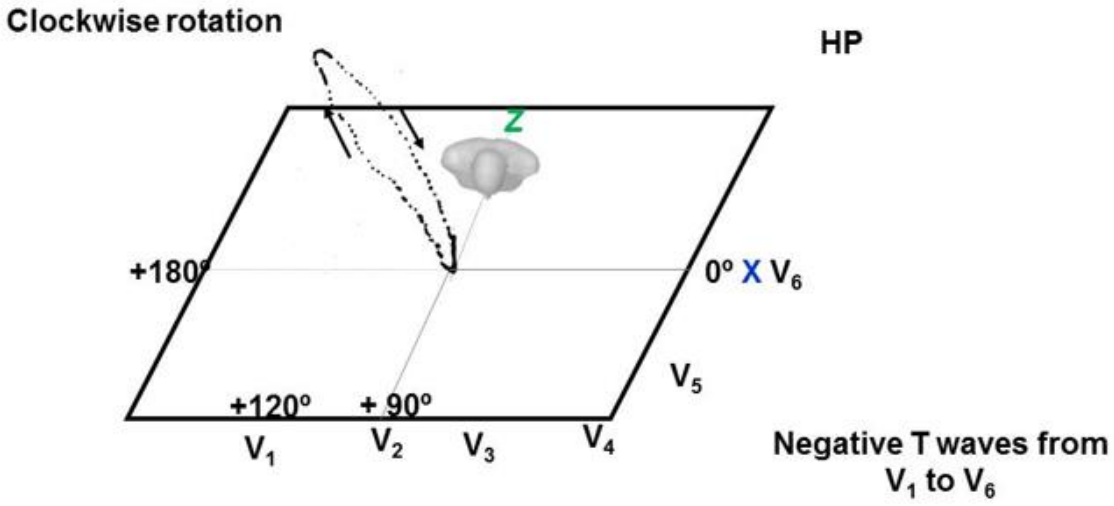


Figure 103. When the RV end diastolic volume is large (in average 320 ml/m2), the T loop displays clockwise rotation in the HP and is located in the right posterior quadrant, which justifies the negative T wave in all precordial leads. Note: the presence of T loop of clockwise rotation, indicates the presence of underlying heart disease.

T loop behavior in ACM and its relationship with RV end diastolic volume

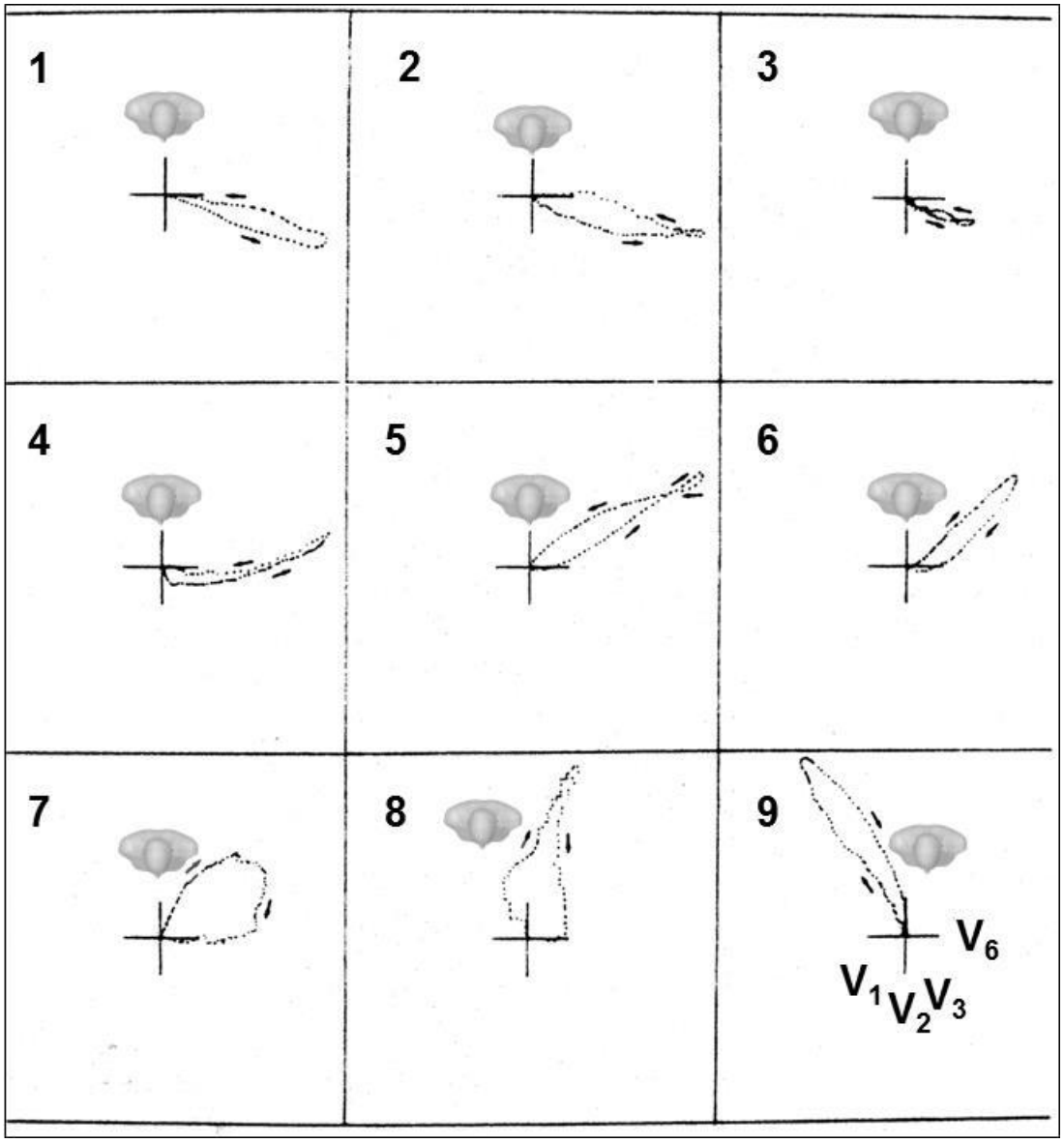


Figure. Negative T waves from V1 to V6. T loop in 9 patients with ACM in the HP. T loops are arranged on the basis of progressive RVH. T loop (nº 1) has a RV end diastolic volume of 100 m^l/m^2 and the last loop (nº 9) has 320 m^l/m^2.[366] Note the progressive alteration of the T loop from 1 to 9.

High resolution ECG in ACM

In ACM, high resolution ECG is frequently associated with late potentials (LP). The ε wave may be observed in surface ECG; however, it is seen much more frequently in high resolution ECG [368].

High resolution ECG is used to detect late potentials (LP) and ε waves in ACM carriers.

Patients with positive high resolution ECG (presence of LP) have statistically significant increase of S-VT and/or SCD in comparison to those with normal high resolution ECG or branch block.

High resolution ECG with LP constitutes a marker of arrhythmic events in patients with non-ischemic dilated cardiomyopathies. On the contrary, patients with dilated cardiomyopathies with normal high resolution ECG, display worsening only if they develop progressive CHF [369].

Fibro-fatty substitution of the myocardium is the substrate of slow and fragmented activation, responsible for the presence of LP.

Abnormal high resolution ECG seems to correlate with the severity of the disease.

High resolution ECG does not seem a sensitive resource in the minor or concealed forms of the disease, since in these patients there is no proper information with this method [370].

The combination of the analysis of time domain and frequency domain of high resolution ECG may be useful for screening patients carriers of ACM. This combination of both domains increases sensitivity without reducing specificity.

Use of filters with a range between 20 and 250 Hz (substituting the classical ranges between 40 and 250 Hz) [371].

The presence of LP in ACM is found in 70% to 80% of cases. These LP may identify patients with a tendency to develop VT runs in little apparent or restricted forms, and it serves to differentiate them from benign RVOT idiopathic VT, with no underlying structural disease. In these cases, high resolution ECG has LP in 0% to 5% of the cases as in normal patients.

When there is SHD, LPs are found in 20% to 40% of cases. In doubtful cases, invasive studies are necessary to rule out a limited form of cardiomyopathy [372].

In absence of branch block, the presence of LP in high resolution ECG is proportional to the size of the RV cavity, and thus is parallel to RV dysfunction [373].

In order to study the differences between benign repetitive MVT that originate in the RV and the VT from ACM, ECG during the event and high resolution ECG may be helpful.

ECG during VT and high resolution ECG may be useful to differentiate both entities. In the case of ACM, VT presents QS in V1 and QRSD related to the amount of fibrous tissue existing in the RV.[374]

There are significant differences for filtered and non-filtered QRS, low duration sign, and square root. In the absence of CLBBB, these differences become non-significant for filtered or non-filtered QRS.[374]

There is a narrow correlation between the result from high resolution ECG and the extension of the disease, with the presence of VT.

High resolution ECG is not a valuable resource in minor forms of the disease, but as this is a noninvasive method, it may be useful to assess the progression of the disease.[375]

In comparison to 12-lead ECG, high resolution ECG detects abnormalities at higher rates in patients with ACM (57% vs. 86%). High resolution ECG is more sensitive as screening test than 12-lead ECG to detect patients with ACM.[376]

The anatomopathological process of ACM also considers late ventricular potentials, which when they are registered as LP in high resolution ECG, indicate electrical stability worsening associated to rapid progression of high resolution

ECG, while clinical parameters remain unchanged. This fact suggests that progression parameters in high resolution ECG are markers of electrical instability increase.

Sensitivity, specificity, predictive value and accuracy of the different criteria of high resolution ECG were estimated in comparison to SMVT inducibility. Filtered QRS duration (fQRS) in high resolution ECG is considered as predictive for the result of the electrophysiological study and ACM evolution [182].

The average of presence of late potentials in ACM is between 70-80%, with extreme values of 47-100%. The latter percentage is observed in severe forms and with documented spontaneous VT.

High resolution ECG is a very useful resource to follow the evolution of the disease.

In relatives of patients, high resolution ECG presents a positivity of LP between 4-16%.

Detecting posterior potentials improves by using 25 Hz filters and specificity is better observed in the orthogonal lead Z.

High resolution ECG should be considered a standard test in the study of patients with suspicion or carriers of ACM;

Future research is necessary to confirm the value of high resolution ECG as predictor of arrhythmic risk and determining factor of progression of the disease, as well as to study the prevalence of high resolution ECG in relatives of patients, thus allowing early detection;

We hope that multidisciplinary continuing studies on ACM will help to answer some of these questions.[182]

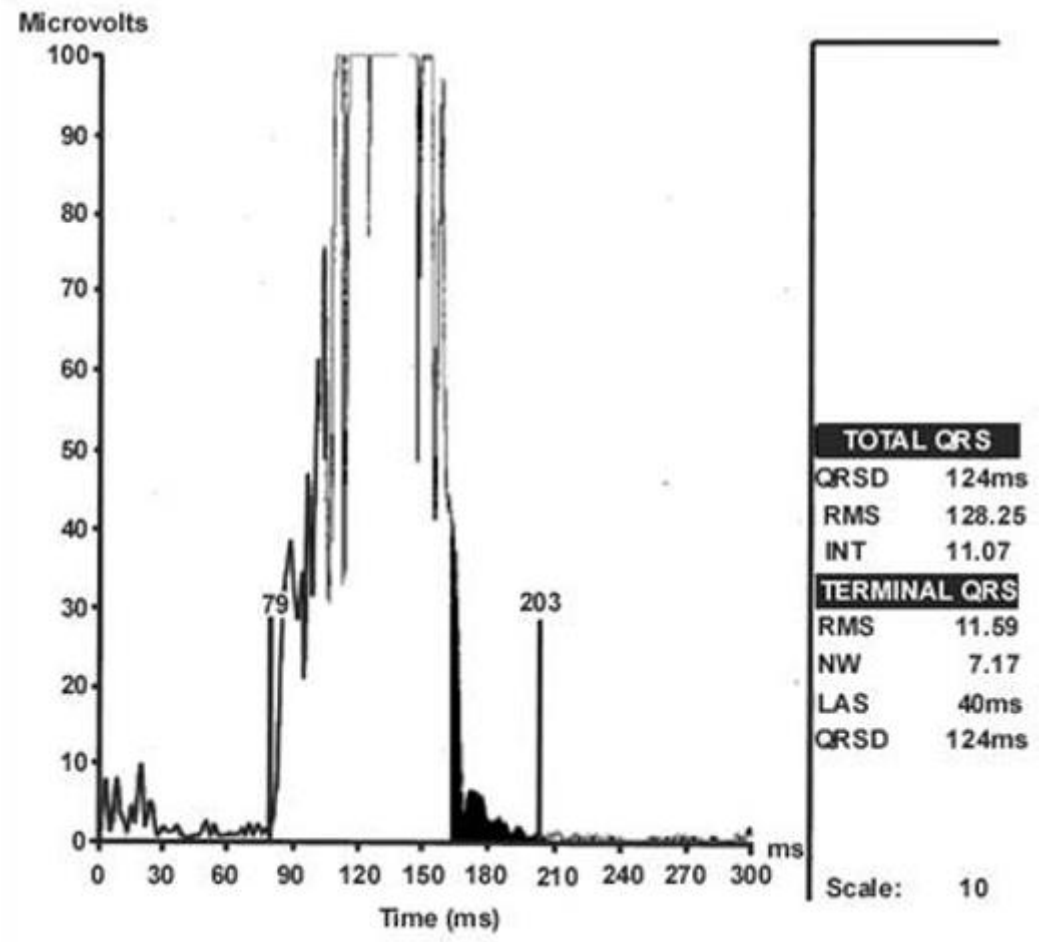


Figure. High resolution ECG with LP (QRSD: 124 ms, LAS: 40 ms, RMS: 11,59 μV).

The Revised TFC for ARVD / ARVC[350, 377]

Major	Minor
2D echo	
Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m2)	Regional RV akinesia or dyskinesia and 1 of the following (end diastole): PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥16 to <19 mm/m2)

PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m2) or fractional area change ≤33%	PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥18 to <21 mm/m2) or fractional area change >33% to ≤40%
MRI	
Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: • Ratio of RV end-diastolic volume to BSA ≥110 mL/m2 (male) or ≥100 mL/m2 (female) or RV ejection fraction ≤40%	Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: • Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m2 (male) or ≥90 to <100 mL/m2 (female) or RV ejection fraction >40% to ≤45%
RV angiography	
Regional RV akinesia, dyskinesia, or aneurysm	

II. Tissue characterization of wall

Major	Minor
Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty	Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or

replacement of tissue on endomyocardial biopsy.	without fatty replacement of tissue on endomyocardial biopsy.

III. Repolarization abnormalities

Major	Minor
Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete RBB QRS ≥120 ms).	Inverted T waves in leads V_1 and V_2 in individuals >14 years of age (in the absence of complete right bundle-branch block) or in V4, V5, or V6. Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals >14 years of age in the presence of complete RBBB.

IV. Depolarization/conduction abnormalities

Major	Minor
Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V_1 to V_3)	Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG
	Filtered QRS duration (fQRS) ≥114 ms
	Duration of terminal QRS <40 µV (low-amplitude signal duration) ≥38 ms
	Root-mean-square voltage of terminal 40 ms ≤20 µV

	Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R´, in V_1, V_2, or V_3, in the absence of complete right bundle-branch block

V) Ventricular Arrhythmias

Major	Minor
MSMVT or SMVT of LBBB morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	Non-SVT or S-VT of RV outflow configuration, LBBB morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis >500 PVCs per 24 hours (Holter)

VI. Family history

Major	Minor
ACM confirmed in a first-degree relative who meets current TFC	History of ACM in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current TFC.
ACM confirmed pathologically at autopsy or surgery in a first-degree relative	Premature sudden death (<35 years of age) due to suspected ACM in a first-degree relative

Identification of a pathogenic mutation† categorized as associated or probably associated with ACM in the patient under evaluation	ACM confirmed pathologically or by current TFC in second-degree relative

PLAX indicates parasternal long-axis view; RVOT, RV outflow tract; BSA, body surface area; PSAX, parasternal short-axis view; aVF, augmented voltage unipolar left foot lead; and aVL, augmented voltage unipolar left arm lead.

Diagnostic terminology for original criteria: This diagnosis is fulfilled by the presence of 2 major, or 1 major plus 2 minor criteria or 4 minor criteria from different groups. Diagnostic terminology for revised criteria: 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.

∗ Hypokinesis is not included in this or subsequent definitions of RV regional wall motion abnormalities for the proposed modified criteria.

† A pathogenic mutation is a DNA alteration associated with ACM that alters or is expected to alter the encoded protein, is unobserved or rare in a large non–ACM control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree. E.g.: in TMEM43, DSP, PKP2, DSG2, DSC2, JUP.

ACM clinical phases

Concealed phase	**Subtle structural changes within the RV, Usually no symptoms, May have minor VT. High risk of SCD.**
Overt phase	Noticeable structural/functional changes within the RV, Symptoms ventricular dysrhythmias, presyncope, syncope, palpitations
Weakening of RV	RV dilates and weakens, RV failure symptoms: edema of legs or ankles, abdominal distension, dyspepsia, anorexia
Weakening of LV	LV dilates and weakens, HF Symptoms: dyspnea on exertion, orthopnea, breathlessness.

Table: Source: Cardiomyopathy Association (http://www.cardiomyopathy.org)

Prognosis

Improving the specific prediction of SCD in ACM can help in patient selection for ICD implantation. Life-threatening ventricular arrhythmia (LTVA); SCD, aborted SCD, VT >250 beats per minute/VF) might have different mechanisms and thus different predictors versus stable ventricular arrhythmia in ACM.

LTVA events can be predicted by a new prediction model that can be easily applied to clinical practice. LTVA events in patients with ACM can be predicted by a novel simple prediction model using only 4 clinical predictors for LTVA events:[378]

1. Age at diagnosis: younger age;
2. Male sex;
3. PVC count (burden of ventricular ectopy);

4. Number of leads with TWI. TWI in 2 of 3 inferior leads, T wave inversion ≥ 3 precordial leads.

Prior sustained VA and the extent of functional heart disease are not associated with subsequent LTVA events. As opposed to stable arrhythmia, LTVA events are not predicted by prior sustained arrhythmic events and the extent of functional alteration of either ventricle. This multivariable risk prediction models (arvcrisk.com) that combine the abovementioned risk factors to estimate individual risks. The flow charts and prediction models require clinical validation studies to determine which should be recommended.

Fibrofatty replacement detected by LGE or T1 mapping in CMRI as criterion for diagnosis is increasingly suggested but requires more supporting evidence from consecutive patient cohorts. In addition to the traditional right-dominant ARVC, standard criteria for ACM and ALVC) are on the horizon. After diagnosis confirmation, the primary management goal is SCD prevention, for which an ICD is the only proven therapy. Prior studies determined that younger age, male sex, previous (non-) SMVT, syncope, extent of TWI, frequent PVCs and lower biventricular ejection fraction are risk factors for subsequent events. Previous ICD indication guidelines were however limited to three expert-opinion flow charts stratifying patients in risk groups.

ARVC Risk Calculator

The ARVC risk calculator is based on clinical data of patients fulfilling ARVC diagnosis as per modified Task Force Criteria[350] from 14 academic centers worldwide. The calculator utilizes two prediction algorithms. One algorithm

predicts the risk of fast VT (>250bpm), VF, or SCA/SCD.[378] The other predicts the risk of any type of sustained VA (including VT <250 bpm) but only the risk of a first event, thus this result should be ignored if the patient had a prior sustained event. It should be stressed that neither of the predicted outcomes estimate the risk of SCD in specific. As the main purpose of ICD implantation is SCD prevention (not VT termination), this is an important limitation when using this calculator for ICD consideration.[379]

Consider the following limitations:

– Risk of *first* Sustained VT predicts only the *first* event, in case of prior sustained events these predictions are not valid and users should ignore these results.

– The calculator is designed to provide predictions based on the clinical characteristics of ACM patients at time of their diagnosis (as per 2010 TFC)

– Caution should be exercised when interpreting the result for pediatric patients <14 years of age, patients with non-classical (RV-dominant) ACM, and carriers of pathogenic variants in less prevalent genes (e.g. TMEM43, DSP, etc)

For more detailed information, read also the sustained VA prediction model publication[379] and the fast VT/VF/SCA prediction model publication.[378]

Management/Treatment

The main goal of ACM management is to prevent or decrease SCD and compensation of CHF.

Management of CM includes lifestyle changes pharmacologic approach, combined endocardial/epicardial catheter ablation, ICD implantation and surgery (Cardiac transplantation).

Lifestyle changes

In addition to medication and devices, there may be ways to reduce the effect of ACM through lifestyle. The following are examples of what might help.

- Minimize caffeine It can raise heart rate and increase blood pressure. As everyone is different in how they react to it, you might like to talk to specialists about how to manage caffeine intake.
- Stopping smoking It is important to help overall health as well as heart and lung function (as it can reduce oxygen levels in the blood as well as narrowing blood vessels).
- Healthy eating – a balanced diet can help to keep a healthy weight, which will reduce the impact on the heart as well as helping with general health.
- Keeping a healthy weight – as this can help to reduce any extra pressure on the heart and lungs.
- Minimize alcohol – alcohol can raise heart rate and increase blood pressure. Patients may not need to completely avoid it, but keeping within recommended guidelines can reduce any potential affects.
- Exercise

Although exercise is often recommended for people with a heart condition, it can trigger arrhythmias and CHF symptoms, and can be dangerous if the condition is unstable. Exercise for people with ACM needs to be considered carefully, and be part of a discussion between the individual and their cardiologist or specialist

nurse. Strenuous exercise can induce MACE, manifesting at an earlier age and promoting the disease progression due to RV dilation with increased risk SCD.[236] It is significantly higher among competitive athletes compared with either recreational athletes or sedentaries.[380] Exercise leads to disruption of cellular junctions by increasing myocardial stress accelerating disease progression. Endurance and frequent exercise increase the risk of VA in patients with ACM. Any competitive sport or activity that causes symptoms in ACM patients should be prohibited (Class I) and physical exercise should be minimized with an exception of low-intensity recreational sports (class IIa) Athletes with syncope be evaluated by an electrophysiologist prior to resuming competitive sports (class I). Assessment by an electrophysiologist is reasonable for athletes with syncope and high-risk markers such as electric instability, frequent PVCs and sustained ventricular arrhythmia, extended TWI, extent of structural disease, cardiac syncope, male sex, multiple mutations (class IIa). Family members of ACM patients be restricted in participation in competitive sports (class IIa).[381, 382]

Psychosocial stress (PSS), such as exercise, can precipitate SCD or CHF progression in patients with ACM. can also increase ACM disease progression is unexplored. Here, Agrimi J et al first quantified perceived stress levels in patients with ACM and found these levels correlated with the extent of arrhythmias and cardiac dysfunction. To determine whether the observed correlation is due to causation, the authors inflicted PSS-via the resident-intruder (RI) paradigm-upon Desmoglein-2 mutant mice, a vigorously used mammalian model of ACM. They found that ACM mice succumbed to abnormally high in-trial, PSS mortality. Conversely, no SCDs occurred in wildtype (WT) counterparts. Desmoglein-2 mice that survived RI challenge manifested markedly worse cardiac dysfunction

and remodeling, namely apoptosis and fibrosis. Furthermore, WT and ACM mice displayed similar behavior at baseline, but Desmoglein-2 mice exhibited heightened anxiety following RI-induced PSS. This outcome correlated with the worsening of cardiac phenotypes. Their mouse model demonstrates that in ACM-like subjects, PSS is incisive enough to deteriorate cardiac structure and function per se, i.e., in the absence of any pre-existing anxious behavior. Hence, PSS may represent a previously underappreciated risk factor in ACM disease penetrance.[383] Exhaustive exercise in ACM patients leads to markedly increased risk of SCD and disease progression. Disease progression is thought to be related to repeated mechanical stress from exercise that may accelerate myocyte cell death due to defective myocyte cell-cell adhesion.[214] Guidelines recommend cessation of competitive and endurance sports in patients with definite ACM (Class I) with the possible exception of recreational low-intensity sports (Class IIa). Restriction from competitive sports may be considered in phenotype-negative family members with a known pathogenic mutation (IIa) or an unknown genotype (IIb). In general, patients are encouraged to refrain from vigorous high intensity exercise, but up to modest exercise is probably reasonable.

Drugs or pharmacological approach

Medical therapy for ACM-related VT is suboptimal. Several drugs can be used:

- **ACE inhibitors (angiotensin-converting enzyme inhibitors)**

Relax the smooth muscle around the blood vessels to reduce the workload on the heart, and reduce the volume of the blood, making it easier for the heart to work.

The BRAVE study was the first randomized controlled trial for drug therapy in ACM patients. This study will be prospectively registered, robustly conducted, independently monitored, rigorously analyzed, and transparently reported. A decrease in RV and/or LV deterioration and in arrhythmia burden are expected in ACM patients treated with ramipril. This reduction will improve quality of life of patients and will reduce the number of hospitalizations and the risk of terminal CHF. The results of BRAVE provide evidence regarding whether ACEI is beneficial to RV function (improvement/stabilization) and improves other important parameters including laboratory (collagen turnover) and clinical outcomes (hospitalization rates, arrhythmias). It will clarify whether the benefits of this intervention outweigh the risks. It is therefore hoped that this pivotal trial can provide new findings to allow future consideration of a large randomized controlled trial with mortality outcomes in this important group of patients.[384]

- **Angiotensin II Receptor Blockers (ARBs)**

Dilate (enlarge) the blood vessels which helps to reduce blood pressure and may be used if the person is not able to tolerate ACE inhibitors.

- **Antiarrhythmic medication**

Reduces abnormal heart rhythms and helps to control the normal rhythm. Although only ICDs have been demonstrated to affect patient mortality, antiarrhythmic medications are important adjuncts in reducing patient morbidity and inappropriate ICD therapy.[385]

- **β-blockers (BBs)**

Reduce the rate and force of the heart's contraction, by reducing stimulation of adrenalin (which would normally make the heart beat faster). BBs are recommended for patients with ACM who develop symptomatic CHF (class I) BB

has been used in ACM patients with VA, supra-VT, or AF/flutter with high-ventricular rate (class I).[145]

BBs are not recommended in asymptomatic healthy patient with gene carriers (Class III).[145] BBs have shown to be effective in reducing adrenergically stimulated arrhythmias. The BB sotalol, and amiodarone appear to be most effective in arrhythmia suppression.[385, 386] However, the available evidence for ACM patients is from observational studies, which have shown conflicting results.[387]

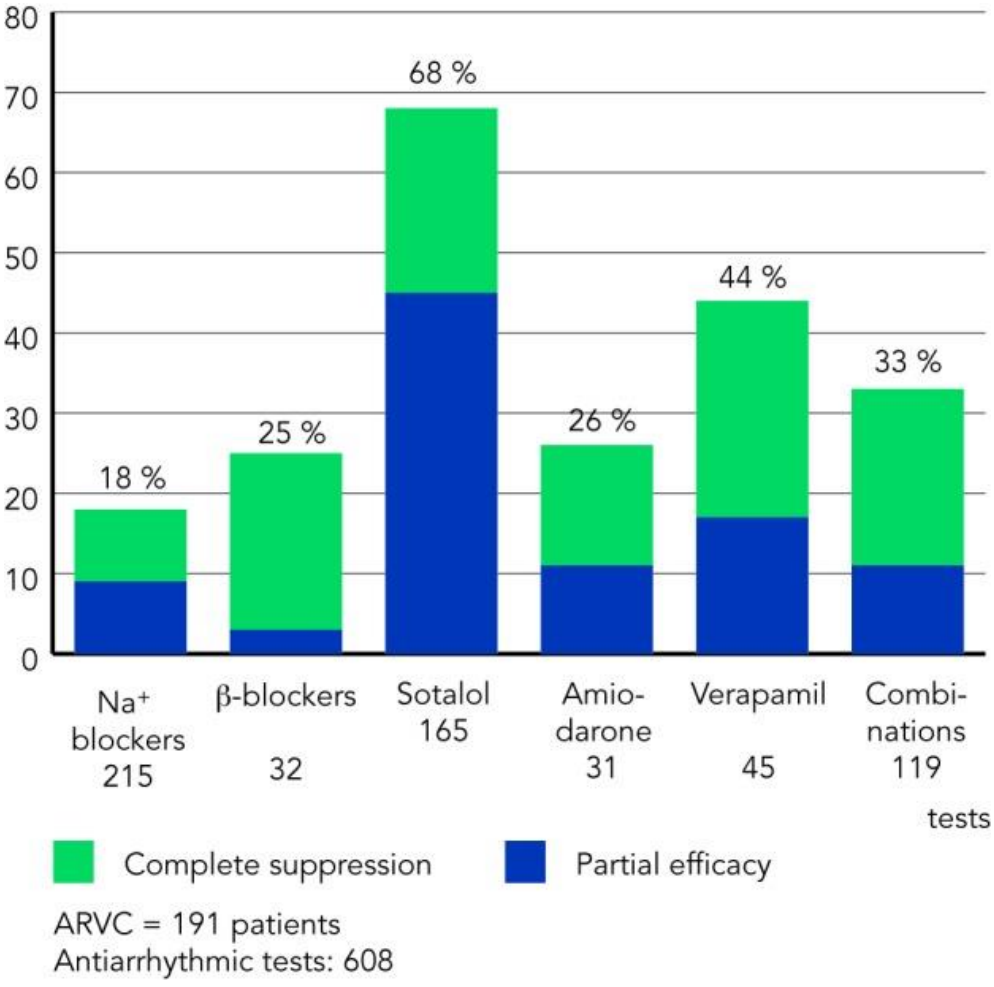
Sotalol is a BB and a class III antiarrhythmic agent, the most effective antiarrhythmic agent in ACM. Sotalol has the FDA and non-FDA indications for PVCs, hemodynamically stable VT, pharmacological cardioversion of AF, maintaining sinus rhythm, postoperative AF after cardiac surgery, supraventricular tachycardia, especially when administered intravenously.

Sotalol is an ethanolamine derivative with Class III antiarrhythmic and antihypertensive properties. It is a methane sulfonanilide beta adrenergic antagonist used to treat life-threatening ventricular arrhythmias and to maintain sinus rhythm in AF or flutter. Sotalol is a non-cardioselective BB with additional potassium channel blocker properties. (potassium channel antagonist). It classifies as a class III agent in the Vaughan-Williams classification system for antiarrhythmic medications due to its predominant potassium channel blocking effect. Sotalol prolongs the action potential duration and effective refractory period in the atrium and ventricle and in nodal and extranodal tissue, as it is a potent competitive inhibitor for potassium current. Sotalol exhibits reverse use-dependent effects, meaning that the maximal potassium current blocking effect occurs when the heart rate is slow, increasing the risk of QT prolongation and

TdPs in bradycardic conditions. A low dose is enough to exert a beta-blocking effect. For example, 25 mg offers good beta-blocking activity, but for class III antiarrhythmic effects, a higher dose is necessary, in the range of 80 mg.

Other antiarrhythmic agents used include amiodarone and conventional BBs (i.e.: metoprolol). If antiarrhythmic agents are used, their efficacy should be guided by series ambulatory Holter monitoring, to show a reduction in arrhythmic events.

Comparative efficacy of antiarrhythmic therapy in patients with ACM[388]



In a large cohort of ACM patients with a long-term follow-up, only BBs administrated at >50% target dose were associated with lower risk of SCD/recurrent major ventricular arrhythmias.[389] Patients in whom BBs were

titrated at >50% of target dose showed marked reduction in risk compared to those not taking BBs (HR 0.10, 95% CI 0.02–0.46, $p = 0.004$). Adequately titrated BBs represent the most promising pharmacological strategy to reduce arrhythmic burden and likelihood of MACE in ACM.[390]

Anticoagulants (blood thinners): Thromboembolic complications, treatment consists of current therapy for CHF including anticoagulant therapy. Patients in whom ACM leads to progressive RV or biventricular systolic dysfunction, treatment consists of pharmacologic therapy for HF including diuretics, angiotensin-converting-enzyme inhibitors, digitalis, as well as anticoagulant therapy.[391]

Anticoagulants may be used in people with arrhythmias to reduce the risk of blood clots forming, which could lead to a stroke. ACM may be complicated by thrombosis. Annual incidence of such complications is significantly lower than reported for LV failure. Anticoagulation should be used in ACM patients with large, hypokinetic RV and slow blood flow.

Patients with severe forms, thrombus formation in the RV and/or spontaneous echocardiographic contrast are at higher risk of a poor outcome.[392] Diuretics reduce the build-up of fluid on the lungs or the ankles by encouraging the kidneys to get rid of water as urine.

Combined endocardial/epicardial radiofrequency catheter ablation: Catheter ablation in ACM is not curative and it does not prevent SCD, it improves quality of life by decreasing the frequency of ventricular arrhythmias.[214, 393] It is recommended in patients with incessant VT or frequent ICD interventions despite maximal pharmacological therapy (Class I). An epicardial approach is recommended for those who fail one or more attempts at endocardial ablation,

where that expertise exists (Class I). This resource may be used to drugs refractory or incessant ventricular tachycardia. RFCA is appropriate as a first approach for endocardial VT ablation in ACM; however, its effectiveness has a low success rate with less than 40% at the first session. Endocardial VT ablation in this setting can produce acute success, though recurrence rate is quite high, which may be explained by the more epicardial and patchy nature of the disease In other words a more extensive epicardial (Epi) arrhythmogenic substrate could explain the low efficacy. Combined endocardial/epicardial mapping reveals a wider (Epi) VT reentrant circuits created by patchy scar formation. with clinical VTs. As a first-line therapy, combined Endo and Epi VT ablation incorporating scar dechanneling (or homogenization of the scar) achieves a very good short- and midterm success rate.[394, 395] Conducting Channels, The CCs have been defined as pathways of orthodromically activated sites inside the scar. In the present study, CCs were identified during stable sinus rhythm. Those CCs between 2 confluent scar areas or between a scar and the tricuspid annulus were considered in addition to intrascar CCs. Scar CCs were identified by (1) a color-coded voltage map adjustment of the lower and upper thresholds (voltage channels) and (2) the presence of 2 tagged recordings of E-IDCs, with the delayed component showing sequential orthodromic activation (late potential [LP] channels) (Figures 1– 4). After CC identification, the entrance of each CC in the scar was tagged during sinus rhythm. The CC entrance was defined as the E-IDC with the shortest delay between the far-field component of healthy muscle (usually low frequency, high voltage) and the local component (delayed activation, usually with fractionation and low voltage) corresponding to the activation of myocardial tissue in the scar.

Fulguration is effective for VT ablation and should be used in the same session after ineffective RFCA. However, fulguration requires expertise, general anesthesia, and more than one session in half of all patients.[396]

It is 60 to 90% successful. Recurrence rate is 60% due to the progression of the disease.

RFCA of VT in ACM patients should be considered a potentially effective strategy for eliminating frequent VT episodes and ICD shocks rather than a curative therapeutic approach, until long-term efficacy has been consistently documented. Research into the optimal mapping and ablation techniques are promising and ongoing.

Prevention of Primary Manifestations: Prospective randomized trials have not been conducted in ACM for the prevention of arrhythmias. Management relies on personalized recommendations based on clinical assessment.

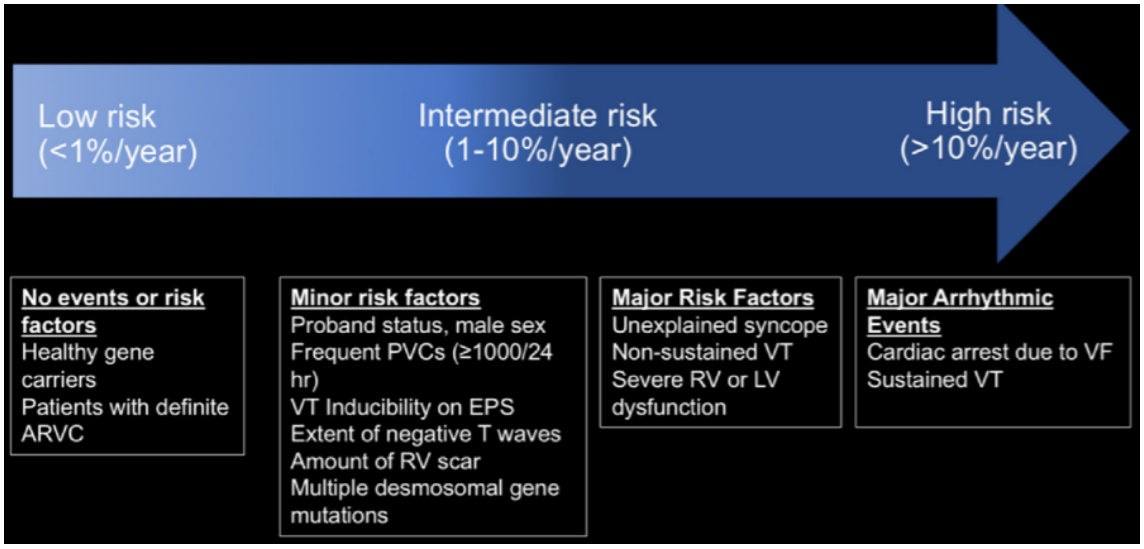
Implantable cardioverter-defibrillators (ICDs): Observational studies support that ICD placement is effective in reducing the risk for SCD in ACM. ICD placement should be considered in anyone with a clinical diagnosis of ACM.[397] Reported results of ICD implantation in 106 individuals with ACM who met task force criteria. Device placement was based on the presence of arrhythmia risk factor defined as syncope, family history of SCD, NS-VT, and whether VT/VF was inducible in an electrophysiology done at the time of device implant. Over the follow-up interval of 58 months, 24% of subjects had an appropriate ICD discharge. Syncope was found to predict appropriate ICD discharge. The advisability of placing an ICD for primary prevention remains a question of debate.[398]

The ACC/AHA (American College of Cardiology / American Heart Association) and European Society of Cardiology (ESC) guidelines:

Class I indication (i.e., procedure/treatment **should** be performed) ICD implantation for prevention of SCD in individuals with documented S-VT/VF who have a reasonable expectation of survival with good functional status for more than one year.

Class II indications (i.e., it is **reasonable** to perform procedure/treatment) for ICD implantation include extensive disease (e.g., LV involvement), family members with SCD, or undiagnosed syncope when VF/VT cannot be excluded as the cause of syncope while the individual was on optimal medical therapy.[399, 400]

Risk Stratification for ACM to help guide decision for ICD implantation.



Patients can be broadly classified into those with high, intermediate and low risk for recurrent VA, to help guide decision for ICD implantation. From Corrado et al. [3]. Abbreviations: ACM, arrhythmogenic cardiomyopathy; VA, ventricular arrhythmia; ICD, implanted cardioverter defibrillator.

Complications of implantable cardioverter-defibrillator treatment in ACM

In a multinational cohort with long term follow-up, Christensen et al describing the complications associated with ICD treatment.[401] The authors included 299 patients (66% males, median age 41 years). During a median follow-up of 10.6 years, 124 (41%) they observed:

- Appropriate ICD shock therapy, 28 (9%)
- Inappropriate shocks, 82 (27%) 3.4% during the first year after implantation but decreased after the first year and plateaued over time. In multivariate cox regression, presence of AF/flutter was a risk factor for inappropriate shock ($P < 0.05$), whereas sex, age at implant, and device type were not (all $P > 0.05$).
- Complication requiring surgery (mainly lead-related, $n = 75$), the risk of a complication requiring surgery was 5.5% the first year and remained high throughout the study period.
- Both inappropriate shocks and surgical complications 99 (33%).
- The combined risk of any complication was 7.9% the first year.
- A third of the patients experienced a complication during follow-up with lead-related complications constituting the vast majority.
- Forty-one percent of ARVC patients treated with ICD experienced potentially life-saving ICD therapy during long-term follow-up.

Surgery

Cardiac transplantation: It is usually indicated as the last resort for ACM patients with severe CHF or recurrent episodes of VT and VF despite RFA, surgical ablation, and ICD placement.[145] In a prospective study Tedford et al observed 18 patients with 1-year survival rate as 94% and 6-year survival rate as

88% following cardiac transplantation.[402] Patients who received transplantation had a more prolonged course of the disease and a relatively early onset compared with those not receiving transplantation.[403]

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