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Novel approaches using electrocardiographic imaging for early detection of ARVC in patients and relatives and symptoms preceding sudden death

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Abstract

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Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is an inherited disease of the myocardium, predominantly affecting the right ventricle (RV). Arrhythmias are common among patients with the disease and Sudden Cardiac Death (SCD) can occur even in early stages.

The overall purpose of this thesis was to investigate the effectiveness of new diagnostic methods in detecting early abnormalities in genetically predisposed individuals and to emphasize the importance of early diagnosis.

The analysis of body surface mapping (BSM) signals recorded using a 252-lead vest revealed abnormal repolarisation patterns in all ARVC patients, but also in 25% of family members who were carriers of the family pathogenic variant (M-carriers). The abnormal repolarization patterns preceded repolarization abnormalities on 12-leads electrocardiogram (ECG). Depolarization abnormalities were also detected by the analysis of body surface signals. The QRS dispersion calculated by the body surface signals was significantly higher among ARVC patients compared with controls. 20% of M-carriers presented also with a slightly elevated QRS dispersion. ECG based QRS dispersion could not adequately differentiate ARVC patients from controls. Thus, the higher resolution of the BSM system permitted the detection of repolarization and depolarization abnormalities even in early stages of the disease.

The analysis of reconstructed epicardial signals using Electrocardiographic Imaging (ECGI) revealed terminal ventricular epicardial activation (the last 20msecs) located only in parts of RV, as opposed to controls, where the right ventricular outflow tract (RVOT) and cardiac base (both right and left ventricle) were activated last. The total ventricular activation time and the RV activation time were both longer in ARVC patients, whereas the area activated during the last 20 msecs was smaller. Similar pattern with delayed conduction in limited areas of the RV were also observed in 50% of the M-carriers. This subgroup presented also smaller area of terminal ventricular activation and longer RV activation time, but the total ventricular activation was normal.

Through nationwide registries, the first SCD cohort due to ARVC in Sweden was described. Cardiac related symptoms were common (68%) prior to death and 36% of cases had sought medical care the last six months prior to death. A family history of SCD was present in 45% of the cases. The careful clinical evaluation of young individuals seeking with cardiac related symptoms and the evaluation of both medical and family history is crucial.

In conclusion, new technologies, using multiple electrodes for the recording of body surface signals and the reconstruction of the epicardial signals have shown promising results in detecting early repolarization and depolarization abnormalities and could facilitate the early diagnosis in M-carriers.

Keywords: Arrhythmogenic Right Ventricular Cardiomyopathy, diagnosis, gene carriers, body surface mapping, electrocardiographic imaging, sudden cardiac death

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Κάλλιον το προλαμβάνειν ή το θεραπεύειν.
Prevention is preferable to cure.

(Hippocrates)

Intellectuals solve problems; geniuses prevent them.

(Albert Einstein)

To my husband Panagiotis
and my sons Dionysis and Jannis,
the joy of my life

List of Papers

This report is based on the following papers, which are referred to in the text by their Roman numeral:

I. Varvara Kommata, Elena Sciaraffia, Carina Blomström-Lundqvist. Repolarisation abnormalities unmasked with a 252-lead Body Surface Mapping system in patients with ARVC and healthy Gene Carriers. Pacing Clin Electrophysiol. 2022; 45(4):509-518

II. Varvara Kommata, Marwa Elshafie, Elena Sciaraffia, Mauricio Perez, Robin Augustine, Carina Blomström-Lundqvist. QRS dispersion detected in ARVC patients and healthy gene carriers using 252-leads body surface mapping: an explorative study of a potential diagnostic tool for arrhythmogenic right ventricular cardiomyopathy. Pacing Clin Electrophysiol. 2021; 44(8):1355-1364.

III. Angelica M. Delgado-Vega, Varvara Kommata, Bodil Svennblad, Aase Wisten, Emil Hagström, Eva-Lena Stattin. Family History and Warning Symptoms Precede Sudden Cardiac Death in Arrhythmogenic Right Ventricular Cardiomyopathy (From A Nationwide Study in Sweden). Accepted. American Journal of Cardiology.

IV. Varvara Kommata, Elena Sciaraffia, Carina Blomström-Lundqvist. Epicardial conduction abnormalities in patients with Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) and mutation positive healthy family members – a study using electrocardiographic imaging. Submitted

Contents

Abbreviations

2D	Two dimensional
3D	Three dimensional
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
AW	Anterior Wall
BrS	Brugada Syndrome
BSA	Body Surface Area
BSM	Body Surface Mapping
CPVT	Catecholaminergic Polymorphic Ventricular Tachycardia
CT	Computed Tomography
DCM	Dilated Cardiomyopathy
ECG	Electrocardiogram
ECGI	Electrocardiographic Imaging
ECM	Electrocardiographic Mapping System
FAC	Fractional Area Change
ICD	Implantable Cardioverter Defibrillator
IW	Inferior Wall
LBBB	Left Bundle Branch Block
LQTS	Long QT syndrome
LV	Left Ventricle
MRI	Magnetic Resonance Imaging
NPR	National Patient Registry
PLAX	Parasternal long axis
PSAX	Parasternal short axis
RBBB	Right Bundle Branch Block
RV	Right Ventricle
RVOT	Right Ventricle Outflow Tract
SAECG	Signal Averaged ECG
SCD	Sudden Cardiac Death
TAD	Terminal Activation Duration
TFC	Task Force Criteria
VT	Ventricular Tachycardia

1. Introduction

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is an inherited disease of the myocardium[1-3] and characterized by loss of the myocardium of varying degrees with accompanying replacement by adipose or fibro-adipose tissue.[2,4] It typically affects the right ventricle (RV) but can also involve the left ventricle (LV), leading to either bi-ventricular cardiomyopathy or less frequently isolated left ventricular cardiomyopathy (ALVC).[1,2,5-7] The histopathological abnormalities predispose to ventricular arrhythmias (VA) and sudden cardiac death (SCD), even in the early stages of the disease.[2,8-10] Therefore, ARVC is one of the main causes of SCD among the young, accounting for up to 12% in several European cohorts.[11-14] The prevalence of ARVC among athletes with SCD is much higher.[15,16]

Initially believed to be a developmental defect of the right ventricular myocardium, the disease was called Arrhythmogenic Right Ventricular Dysplasia (ARVD). This term, even though questionable, has dominated in the last 40 years. Uncovering the pathophysiology of the disease and realizing its progressive and genetically determined character, the term ARVD was gradually replaced by the most recent Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC). The term Arrhythmogenic Cardiomyopathy (ACM) has recently been proposed in an attempt to cover the whole spectrum of ARVC different genotypes and phenotypes.[17]

The diagnosis of ARVC has evolved over the years. The development of cardiac imaging and genetics has provided new diagnostic possibilities.[18,19] However, the diverse phenotypes encountered in ARVC populations, the slow development of the disease, the low penetrance and the many phenocopies still pose significant diagnostic challenges to the clinicians.[7,20-24] The fact that the most devastating manifestations of the disease, i.e., ventricular arrhythmias and SCD, can occur in early stages, makes early diagnosis mandatory.[8-10] New diagnostic modalities are warranted in order to improve the diagnostic yield of ARVC and identify the individuals at risk, with the ultimate purpose of preventing SCD.

1.1 Historical perspective

The first historical description of ARVC was probably done by Giovanni Maria Lancisi, when he was asked to investigate a mysterious increase in the

number of sudden deaths. Lancisi reported his results in his book "*De motu cordis et aneurysmatibus"* (1736), where he also reported a family with several cases of SCD during four generations and the presence of heart failure, dilatation, and aneurysms of the right ventricle.[25] This was probably the first family with ARVC described in history.

However, ARVC was first recognized as an entity in the late 1970s by Guy Fontaine's group at La Salpetriere Hospital in France, when several patients with drug resistant RV tachycardia underwent open heart surgery with epicardial mapping.[26,27] The co-existence of RV origin of the arrhythmia, RV dilatation, late potentials, and fibrofatty infiltration of the RV was first described.[27] Fontaine introduced the term dysplasia to describe this condition, and the first series of 24 cases with right ventricular dysplasia was reported 1982.[2] All patients in this report presented RV dilatation, precordial T-wave inversion, and late potentials, which were the first diagnostic criteria.

A few years later, further reports from other research groups pointed out the correlation of ventricular tachycardias with left bundle branch block (LBBB) morphology with structural and functional abnormalities of the right ventricle.[8,28-30] Several small cohorts with a few years of follow-up were described, underlining the progressive nature of the disease, the variety of the ventricular arrhythmias observed, and the difficulty of predicting the outcome.[8-10] The hereditary character of the disease was recognized early and determined as an autosomal dominant inheritance in most cases.[3] In 1988, the first cases of familial palmoplantar keratosis with associated cardiac abnormalities were reported.[31,32] The syndrome was named Naxos disease, and it was an autosomal recessive type of ARVC with high penetrance.[31,33]

The first gene suggested to be causative for ARVC was the plakoglobin (JUP) gene in 2000, when a deletion in JUP was detected in several patients with Naxos disease.[34] The recognition of the association of a protein involved in cell-cell adhesion with ARVC played an important role in understanding the pathophysiology of the disease. After the discovery of JUP, the genetic background of ARVC started to get unfolded, and more involved genes were detected.[35-42]

1.2 Epidemiology

The prevalence of ARVC in the general population is estimated to be between 1:1000 and 1:5000.[43-45] ARVC typically presents between the second and fourth decade of life, but late onset of the disease is not uncommon.[21,46-48] The disease affects both men and women, although men tend to develop a more malignant phenotype.[47,49,50] The mechanism of these sex differences is still unclear. It has been suggested that there is a direct influence of the male sex hormone in the pathogenesis of ARVC, as the high testosterone levels in men

with ARVC have been associated with a higher risk of arrhythmic events in a previous study.[51] In another study, frequent endurance exercises, which are more common among men compared to women, have been associated with a higher risk of developing ventricular arrhythmias and heart failure in carriers of desmosomal gene mutations.[52]

2. Etiology

2.1 Genetics

In most cases, ARVC presents an autosomal dominant inheritance with incomplete penetrance.[53-57] Recessive forms are also described, with the most common being Naxos disease and Carvajal syndrome, which are associated with cutaneous disorders and have a higher penetrance.[31,34,58,59] The most common genes associated with ARVC are desmosomal genes, which encode desmosomal proteins. However, many genes associated with other cardiomyopathies or channelopathies are also involved, suggesting an overlapping with other arrhythmogenic conditions and expanding the phenotypic and genotypic spectrum of the disease.[54,55]

2.1.1 Desmosomal genes

Desmosomal genes have been reported in 33% to 63% of probands in various ARVC cohorts, with the most common being plakophillin-2 (PKP-2).[21,56,60-63] PKP-2 mutations are associated with a conventional ARVC phenotype with predominantly RV involvement.[64] Desmoplakin (DSP) mutations are often associated with LV involvement and potentially end-stage heart failure, particularly in cases of non-missense mutations, as well as with a higher risk for ventricular arrhythmias and SCD.[49,65,66] LV is often affected even in ARVC patients with mutations in the desmoglein-2 gene (DSG-2) and desmocollin-2 gene (DSC-2).[21,41,56, 39,67] A recent study reported a higher risk for end-stage heart failure in patients with DSG-2 mutations, but these results have not been confirmed in larger cohorts.[21,68]

Plakoglobin mutations are uncommon and more often associated with Naxos disease.[34] Recessive mutations in DSP gene are associated with Carvajal syndrome, while autosomal dominant DSP mutations have been described in erythrokeratodermia-cardiomyopathy (EKC) syndrome.[59,69] Homozygous mutations of DSC-2 gene have also been reported in ARVC with mild palmoplantar keratoderma and woolly hair.[70]

2.1.2 Non desmosomal genes

Missense variants in ryanodine receptor gene (RYR-2) have been identified in ARVC families and are associated with a conventional ARVC phenotype.[35,71]

Mutations in transmembrane protein 43 gene (TMEM43) have been identified in several ARVC populations and are often associated with early onset, high penetrance, LV dilatation, heart failure and present a high risk for SCD.[72-75] Similarly, mutations in the phospholamban (PLN) gene were encountered in 12% of the ARVC patients in a Dutch cohort and are associated with an increased risk of SCD and heart failure.[76]

Lamin A/C gene (LMNA) and desmin (DES) gene have both been reported in ARVC patients and are associated with a worse prognosis, heart failure, and conduction disease.[77-82] Conduction disorders have also been correlated with missense variants in the titin (TTN) gene, which is also associated with an increased risk of SCD and heart failure.[83] The Sodium Voltage-Gated Channel Alpha Subunit 5 gene (SCN5A), mainly associated with Brugada syndrome, has been found in some ARVC cohorts, suggesting its involvement in ARVC pathogenesis.[84,85,86]

Other non desmosomal genes suggested as being involved in the ARVC pathogenesis are the T-catenin gene (CTNNA3), the cadherin-2 gene (CDH2), the transforming growth factor β3 (TGFβ3), and the tight junction protein 1 gene (TJP1).[40,87-89] These genes have been reported in rare cases; however, their role in ARVC is not yet established.

2.1.3 The role of the desmosomes

The involvement of the desmosomes in the ARVC pathogenesis was first suggested after the detection of the first disease-causing variant of plakoglobin gene in patients with Naxos disease.[34] Immunohistochemical and electron microscopy studies on myocardium from patients with Naxos disease revealed a reduced expression of the gap junction protein connexin 43 and failure of plakoglobin to re-localize at cell–cell junctions, which were fewer and smaller.[90] Similarly, studies in Carvajal syndrome patients revealed that the immunoreactive signal for desmoplakin, plakoglobin, and connexin-43 was markedly diminished at the intercalated discs, while the intermediate filament protein desmin failed to re-localize at the intercalated discs.[91] Similar changes in the various intercalated disc proteins have been presented in more recent studies in patients with typical ARVC due to PKP-2 mutations, suggesting a common pathway for the pathogenesis of the different types of ARVC.[92-94] Finally, the study of the ultrastructural features of the myocardium with a transmission electron microscope revealed intercalated disc remodeling with dislocation and loss of desmosomes in ARVC patients.[95] These findings support the theory that genetic defects in the desmosomes cause a disruption of the intercellular junction, leading to apoptosis and cellular death.[96]

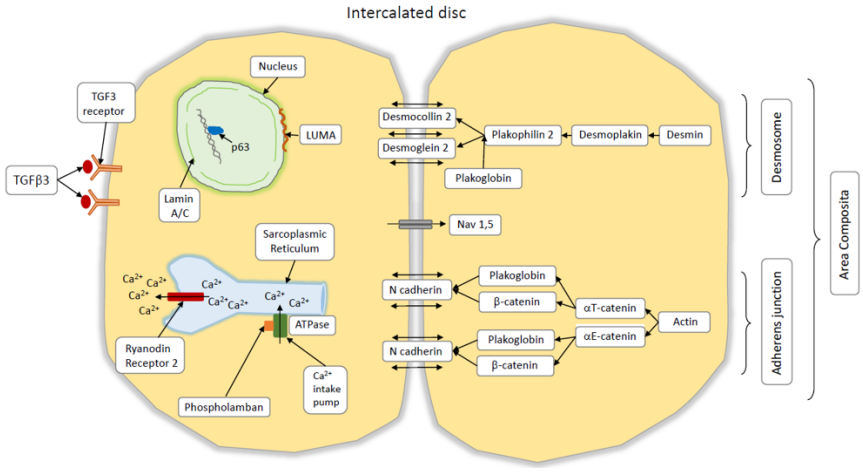

Figure 1. Desmosomal proteins associated with pathogenesis of ARVC.

The figure illustrates the main proteins expressed on the intercalated disc, which are associated with arrhythmogenic right-ventricular cardiomyopathy (ARVC) phenotype, and the way they interact with each other and other proteins of the myocytes. The proteins (genes) associated with ARVC and shown here are: plakophilin-2 (PKP2); desmoglein-2 (DSG2); desmoplakin (DSP); desmocollin-2 (DSC2); plakoglobin (JUP); alpha-T-catenin (CTNNA3); N-cadherin (CDH2); nuclear envelop protein LUMA (TMEM43); Lamin A/C (LMNA); desmin (DES); phospholamban (PLN); ryanodine-receptor type 2 (RYR2); Nav1.5 (SNC5A); P63 (TP63); and TGF-beta 3 (TGFB3).

2.2 Pathophysiology

The main histopathological feature of ARVC is the myocardial loss and replacement by fibrous and/or fatty tissue, which is progressive, starts at the epicardium or midmyocardium and extends to the endocardium, causing transmural lesions.[2,4,7,97,98] Progressive loss of the myocardium leads to wall thinning and aneurysms in the RV, a hallmark for ARVC.[97] Histologic involvement of the LV is often observed even in the absence of macroscopically detectable LV abnormalities.[7]

Various histopathological types of ARVC have been described, with various degrees of fibrous and fatty myocardial infiltration.[11,97] The presence of fatty infiltration of the RV alone has been seen even in normal hearts, in elderly, and in adipositas cordis and is considered unspecific.[99,100,101] The most important parameters for the histologic diagnosis are the residual myocardium and the fibrous replacement of the RV free wall.[19,101]

Focal necrosis, signs of apoptosis, and inflammatory infiltrates are common in myocardial biopsy among ARVC patients.[7,97,102,103] Myocarditis is also

a frequent finding at histologic examinations; moreover, an inflammatory theory has been proposed, suggesting that infective mechanisms may contribute to the onset and progress of the disease.[7,104] Even though cardiotropic viruses have been detected in some studies, the role of viruses in ARVC pathogenesis remains unclear.[104-106]

2.3 Ventricular arrhythmias

Already in the late 1980s, it was hypothesized that the fibrofatty tissue acts as a substrate for ventricular arrhythmias. The delayed and fractionated conduction, as the electrical activation propagates from strands of healthy myocardium to degenerated fibrofatty tissue, is known to create macro-reentrant circuits that promotes ventricular tachyarrhythmias.[98]

In the last few years other mechanisms, operating at the molecular and cellular level, have been proposed.[107-109] The role of the desmosomes and intercalated discs is considered crucial for the arrhythmogenesis. Desmosomes, adherent junctions, and gap junctions are three distinct parts of the intercalated discs, composing a single functional unit.[108] Intercalated disc proteins interact synergistically to regulate cell-to-cell adhesion, excitability, and coupling of myocytes. Loss of expression of intercalated disc proteins induces remodeling of the gap junctions and disturbs the redistribution of other proteins of the intercalated discs, even if their expression is intact.[90-95] Experiments on animals and cellular models have also shown that the loss of desmosome protein expression reduces the Na^+ current and slows the conduction velocity, increasing the arrhythmia susceptibility.[107,109] These results suggest a molecular crosstalk among the components of the intercalated discs, whereby the loss of desmosomal integrity translates into a disruption of the electrical stability of the heart.[107-109]

A molecular mechanism of arrhythmogenesis could probably explain the early occurrence of ventricular arrhythmias, even before structural abnormalities are recognizable.[7,11,12] Consequently, early detection of such early changes on the cellular level, corresponding to the subclinical phases of the disease, is crucial in order to ensure the early management of life-threatening arrhythmias and to prevent SCD.

2.4 The role of exercise

The role of exercise on ARVC progression and arrhythmogenesis has been proposed and emphasized in several clinical and experimental studies.[52,110-114,115-117] In a previous study with healthy endurance athletes, it has been reported that there is a disproportionally greater RV load excess compared to

the LV in athletes but not in controls.[118] It has therefore been proposed that endurance exercise may aggravate the mechanical uncoupling of the myocytes in the RV due to the increased mechanical stress and lead to structural abnormalities.

However, this theory has been questioned, as in experimental studies with myocytes from transgenic mice, mutations in the desmosomal proteins did not affect the cell-to-cell adhesion, although the response to mechanical stress was abnormal.[119] These results suggest another molecular pathway that does not involve the integrity of the intercellular junctions.

3. Clinical presentation and manifestation of the disease

3.1 Clinical manifestations

The most common early manifestations of ARVC are palpitations, dizziness, and syncope, especially exercise-induced.[8-10,46,120,121] Even if uncommon, SCD/ aborted SCD can be the first reported manifestation of the disease.[7,11,12] At the time of diagnosis, the patients may present with electrocardiographic abnormalities and/or ventricular arrhythmias (from ventricular extrasystoles to sustained or non-sustained ventricular tachycardias), and further examination with echocardiography may reveal structural abnormalities at the RV.

Family members may also develop symptoms, particularly those who fulfilled 2010 TFC for ARVC during the first clinical evaluation. Syncope, presyncope, and palpitations are the most common symptoms reported among relatives.[21,122,123]

The most important symptoms and clinical characteristics of ARVC patients and relatives are summarized on table 1.

3.2 Natural history and disease progression

The overt phase of the disease is usually preceded by a concealed phase with minimal or no structural abnormalities.[122] The risk for ventricular arrhythmias and SCD is high even during this early phase of the disease.[7,11,12]

As the disease progresses, RV dilatation and RV wall abnormalities (hypokinesia, dyskinesia, or even aneurysm) develop, and the systolic function of the RV becomes impaired.[21,45,46] Left-dominant variants of the disease are not uncommon, making the differential diagnosis from other cardiomyopathies particularly challenging.[5,6] In more advanced stages of the disease, both ventricles may be affected, leading to biventricular cardiomyopathy and heart failure.[7,120] Cardiac transplantation can be needed in rare cases, predominantly due to heart failure (90%), but even due to ventricular arrhythmias (approximately 10%).[21,125] Many patients have recurrent ventricular arrhythmias, which require treatment with antiarrhythmic drugs.[2,8-10,21] In cases of recurrent ventricular arrhythmias, despite adequate pharmacological treatment,

an implantable cardioverter defibrillator (ICD) may be indicated.[21,126] Ablation of the ventricular tachycardias may also be an option, having good results.[127]

Up to one-third of family members have been reported in different cohorts to develop the disease, with siblings being at the highest risk.[21,122,123] Genotype-positive family members also presented a higher risk for developing ARVC diagnosis, ventricular arrhythmias, or symptoms compared with first grade relatives in genotype-negative families.[21]

Table 1. Clinical characteristics in ARVC

Clinical characteristics of ARVC patients and relatives		
Clinical findings	**Frequency**	
	ARVC patients[6,21,46,121,124]	**Relatives[21,22,122]**
Symptoms		
Symptomatic	56-94%	36-39%
Palpitations	15-67%	28-31%
Syncope (of all causes)	12-33%	12-19%
Presyncope	9-29%	13%
Chest pain	2-27%	Unknown
Ventricular arrhythmias		
>500 PVCs/24h	30-82%	12-16%
Sustained or non-sustained VT	41-79%	3-8%
VT of LBBB morphology	32-79%	Unknown
VT of RBBB morphology	1-11%	Unknown
SCD/ aborted SCD	1-13%	0
ICD	20-68%	
Global or regional dysfunction and structural alterations		
Fulfilling imaging TFC criteria	Up to 67%	2-18%
Severe RV dilatation and RV dysfunction	30-36%	Unknown
RV wall motion abnormalities	47-85%	1-27%
RV aneurysms	10-48%	Unknown
Decreased LV systolic function	2-47%	Unknown
Cardiac transplantation	0-4%	0

The table summarizes the most important clinical characteristics of ARVC patients and relatives during follow-up.

(ARVC: arrhythmogenic Right Ventricular Cardiomyopathy, SCD: Sudden Cardiac Death, PVC: premature ventricular complex, VT: ventricular tachycardia, LBBB: left bundle branch block, RBBB: right bundle branch block, RV: Right ventricle, LV: Left ventricle, TFC: Task Force Criteria)

4. Diagnosis

For many years, the diagnosis of ARVC was based on local protocols and traditions. The first attempt to establish generally approved diagnostic criteria was made in 1994, when an international task force (the Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology) introduced the first guidelines in the form of a scoring system with major and minor criteria.[128] These diagnostic criteria were revised in 2010 to improve the diagnostic sensitivity, especially among family members of affected individuals.[19] The previous qualitative criteria for diagnosing RV abnormalities were replaced by quantitative ones, and genetic criteria were added.

The 2010 TFC are divided into six categories, in each of which there are separate minor and major criteria (Table 2). The definite diagnosis is fulfilled by the presence of 2 major, or 1 major plus 2 minor criteria, or 4 minor criteria from different categories. When 1 major and 1 minor or 3 minor criteria from different categories are fulfilled, the diagnosis cannot be confirmed, but it is characterized as borderline ARVC. The individuals who fulfil 1 major or 2 minor criteria from different categories are characterized as possible ARVC.[19]

4.1 Global or regional dysfunction and structural alterations

Non-invasive cardiac imaging techniques, particularly two-dimensional echocardiography and Magnetic Resonance Imaging (MRI) play an important role in ARVC diagnosis.[18] The anatomy, dimensions, wall motion pattern, and systolic function of the RV can be evaluated with both techniques.[18] The RV wall motion abnormalities (dyskinesia, akinesia, or aneurysm), in combination with RV dilatation or decreased systolic function, are diagnostic criteria, major or minor, depending on the degree of the pathology.[19]

Table 2. Revised Task Force Criteria 2010	
I. Global or regional dysfunction and structural alterations*	
Major	**Minor**
By 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/m^2) — PSAX RVOT ≥ 36 mm (corrected for body size PSAX/BSA ≥ 21 mm/m^2) — *or* fractional area change ≤ 33% **By 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/m^2 (male) or ≥100 mL/m^2 (female) — *or* RV ejection fraction ≤40% **By RV angiography:** ● Regional RV akinesia, dyskinesia, or aneurysm	**By 2D echo:** ● 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/m^2) — PSAX RVOT ≥ 32 to < 36 mm (corrected for body size PSAX/BSA ≥ 18 to < 21 mm/m^2) — *or* fractional area change > 33% to ≤ 40% **By MRI:** ● 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/m^2 (male) or ≥ 90 to < 100 mL/m^2 (female) — *or* RV ejection fraction > 40% to ≤ 45%
II. Tissue characterization of the wall	
● 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	● 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 endomyocardial biopsy
III. Repolarization abnormalities	
● Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals > 14 years of age (in the absence of complete right bundle-branch block QRS ≥ 120 ms)	● Inverted T waves in leads V1 and V2 in individuals > 14 years of age (in the absence of complete right bundle-branch block) or in V4, V5, or V6 ● Inverted T waves in leads V1, V2, V3, and V4 in individuals > 14 years of age in the presence of complete right bundle-branch block

IV. Depolarization/conduction abnormalities	
● Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3)	● 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 V1, V2, or V3, in the absence of complete right bundle-branch block
V. Arrhythmias	
● Non-sustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	● Non-sustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis ● > 500 ventricular extrasystoles per 24 hours (Holter)
VI. Family history	
● ARVC/D confirmed in a first-degree relative who meets current Task Force criteria ● ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative ● Identification of a pathogenic mutation† categorized as associated or probably associated with ARVC/D in the patient under evaluation	● History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets the current Task Force criteria ● Premature sudden death (< 35 years of age) due to suspected ARVC/D in a first-degree relative ● ARVC/D confirmed pathologically or by the current Task Force Criteria in second-degree relative

4.1.1 Echocardiography

The value of echocardiography in ARVC diagnosis, enabling the assessment of RV structure and function, was recognized early on.[129,130] Echocardiography is non-invasive, inexpensive, and widely available and is the first line imaging modality in ARVC diagnosis and follow-up.[18]

The 2010 TFC are based only on the 2D echocardiography and consist of the presence of wall motion abnormalities (dyskinesia, akinesia, or aneurysm), measurements of the RVOT, and the fractional area change of the RV (RV-FAC).[19] The segmental evaluation and measurement of RV are often challenging, due to its anatomy and retrosternal position. More views on the echocardiographic protocol and specific expertise are required to have a correct interpretation.[18,55] Moreover, the echocardiographic 2010 TFC are, in general, highly specific, but they lack sensitivity for early stages of the disease.

New echocardiographic techniques are required in order to improve the sensitivity and effectiveness of conventional echocardiography. *Contrast echocardiography* has been suggested to improve the image quality, but its usefulness has not been systematically evaluated.[131] *Tissue Doppler echocardiography* has revealed a decreased tricuspid annular plane systolic excursion (TAPSE) and peak systolic RV annular velocity in ARVC patients compared to controls, but these changes are usually apparent in advanced stages of the disease.[132-134] The development of *three dimensional (3D) echocardiography* may allow for the measurements of RV volumes and RV ejection fraction, which correlate highly with the MRI measurements.[135] Reference ranges and new software for 3D RV analysis are now available, but no data exist on ARVC populations yet.[136,137]

Using s*peckle tracking echocardiography (STE)*, both the RV global longitudinal strain (RV GLS) and RV free wall strain have been reported to be reduced in ARVC patients, as well as in gene carriers and first-degree relatives of patients with ARVC.[132,134,138-140] Moreover, the 2D strain analysis of gene carriers in different stages of ARVC identified distinct RV deformation patterns, which were correlated to the stage of the disease.[141] The RV mechanical dispersion, a measurement of the heterogeneous contraction of RV, is pronounced in ARVC patients, probably reflecting the electrical dispersion and is associated with a higher risk of ventricular arrhythmias.[142-145] Combining the RV deformation patterns with the RV mechanical dispersion, the correlation with malignant arrhythmias can be significantly increased.[146] In conclusion, speckle tracking echocardiography is a promising method, with good reproducibility and is easily available. However, further research for the establishment of reference ranges is required before it is broadly implemented in clinical use.[147]

4.1.2 Magnetic Resonance Imaging (MRI)

The first description of MRI examination in an ARVC patient dates to 1987, when MRI with spin-echo technique revealed intramyocardial fat deposits in a patient with advanced disease.[148] Two years later, a study of seven ARVC patients demonstrated dysplastic lesions in the right ventricular wall, presenting "fat-like" high signals, detected by MRI.[149] The first review on the usefulness of MRI in diagnosing ARVC was published on 1993, emphasizing the importance of the visualization of fat or extreme thinning in the infundibulum and the inferior or diaphragmatic free wall of the RV.[150]

Even though it is not as easily available and widespread as echocardiography, MRI is commonly used in ARVC diagnosis. The morphology, volume, mass, and wall thickness of the ventricles, as well as the presence of fibrosis, adipose tissue, or edema can be assessed non-invasively.[18,151,152] Due to its high spatial resolution, MRI is considered more accurate and sensitive compared to conventional 2D-echocardiography.[153] It is therefore included in the 2010 TFC for the evaluation of the diameter and RV systolic function.[19]

As the fibrofatty replacement of the myocardium is a pathologic hallmark for ARVC, the first studies with cardiac MRI focused on the detection of fibrous and adipose infiltration within the thin RV wall.[154-158] Several studies have later proposed the detection of fibrosis in ARVC patients using late gadolinium enhancement (LGE) MRI.[159-162] The presence of fat in a RV segment with normal contraction and thickness is unspecific, while the combination of wall thinning, wall motion abnormalities, and fatty infiltration is in favor of ARVC.[163] Thus, the detection of fibrofatty infiltration should be treated with caution in the absence of other criteria. Similarly, the absence of fat in the MRI cannot preclude the diagnosis and should be interpreted in the context of the whole diagnostic work up.[164]

MRI also plays an important role in differential diagnosis, distinguishing ARVC related abnormalities from phenocopies, such as RV volume overload, cardiac sarcoidosis, other cardiomyopathies, or non-ARVC related myocardial scarring.[165,166] The differential diagnosis between ARVC and myocarditis can be particularly challenging.[5]

MRI is the method of choice for the assessment of RV volume and regional function, with a high intra- and inter-observer reproducibility.[167] However, the assessment of wall motion abnormalities is subjective and requires specific expertise.[168] The development of new MRI techniques can further improve its diagnostic capacity. Strain analysis using the feature tracking technique is a promising method, which enables the quantification and objective assessment of wall motion abnormalities with a good reproducibility.[169-172] T1 mapping with gadolinium-enhanced inversion recovery sequences enables the quantification of fibrosis, enabling the detection even of diffuse fibrosis.[173] Although these techniques are still under development, both can potentially play an important role in ARVC management in the future.

4.1.3 Computed Tomography (CT)

The role of CT on ARVC diagnosis has been explored in previous studies, where RV dilatation, wall thinning, wall motion abnormalities, and sub-epicardial fat have been detected with conventional CT.[174-177] Electron-beam computed tomography (EBCT) received considerable attention in previous years because of its good temporal resolution, enabling the quantitative assessment of volumes, mass, and function of both ventricles.[177-179] Nowadays, multidetector CT (MDCT) scanners allow for an improved visualization of the myocardium with excellent spatial resolution and are considered more suitable for the assessment of biventricular tissue involvement.[180-184]

CT is not a part of the ARVC diagnostic work-up so far.[19] The radiation exposure is a limitation for its usage in serial evaluation of younger individuals. However, its advantages compared to MRI, such as the absence of artefacts caused by implantable devices or by frequent ventricular extrasystoles, and its suitability in claustrophobic patients, make the usefulness of CT in evaluation of selected ARVC patients a possibility in the future.

4.1.4 Selective RV angiography

Even if currently not widely used, RV angiography is still included in TFC. RV akinesia, dyskinesia, or aneurysm detected by RV angiography are considered major diagnostic criteria.[185,186]

4.2 Histopathological changes

Even if histopathological abnormalities are included in the 2010 TFC, the role of endomyocardial biopsy in ARVC diagnosis is nowadays limited.[19] The fibrofatty infiltration is more often located in the epicardium of the RV free wall and has a patchy pattern.[98,101] Thus, the diagnostic accuracy of endomyocardial biopsy depends on the location and number of samples obtained, and a negative result cannot preclude a diagnosis of ARVC.[101,187]

Electroanatomic mapping-guided biopsy can probably increase the diagnostic yield by identifying affected areas with low voltage.[188,189] However, performing a biopsy on the thinned RV free wall can endanger the patient's safety.[101,187] Despite these considerations, voltage-guided endomyocardial biopsy may be useful in differential diagnosis in selected cases, ruling out other pathologies, such as sarcoidosis or myocarditis.[190,191]

The histopathologic examination during the autopsy of SCD victims is very important and can establish the ARVC diagnosis. However, the limitations mentioned above regarding the importance of several samples due to the patchy pattern of the disease apply here as well, and a negative autopsy cannot always exclude a diagnosis.

4.3 Repolarization and depolarization abnormalities

The importance of the ECG in ARVC diagnosis was obvious already when the first cases of ARVC were reported in the 1980s.[2] The most frequent abnormality reported was the T-wave inversion in the right precordial leads and the epsilon waves, described as post-excitation waves.[2] The high frequency of ventricular premature complexes, as well as spontaneous ventricular tachycardias, most often with a left bundle branch block pattern were also reported.[2]

ECG abnormalities during sinus rhythm have been established as diagnostic criteria since the first TFC in 1994. The appearance of epsilon waves was considered a major criterion, while repolarization changes, late potentials on Signal Averaged ECG (SAECG), frequent ventricular extrasystoles, and LBBB morphology of ventricular tachycardia were considered minor criteria.[128] Since the revision of the TFC in 2010, the T-wave inversion V1-V3 and beyond, as well as the typical LBBB pattern ventricular tachycardia have been upgraded to major criteria, emphasizing the essential role of ECG in the diagnosis of ARVC.[19] However, a minority of affected patients can present with a normal ECG or nonspecific ECG abnormalities, suggesting that a normal ECG cannot preclude ARVC.[192] The most common ECG findings in ARVC are summarized on table 3.

In an effort to increase the diagnostic and predictive value of ECG, several studies have proposed complex methods for ECG analysis, such as vectorcardiography derivations, the computerized terminal S-wave area in the right precordial leads, or body surface mapping.[193,194,195] Nevertheless, surface ECG remains the only widely accepted and used method.

4.3.1 Repolarization abnormalities

T-wave inversion in precordial leads (V1-V3) is a pathognomonic feature for ARVC[2] (Figure 2). Although seen even in healthy young individuals or athletes to some extent, it is found in up to 87% of ARVC patients.[196-198,200,202] The extent of the precordial T-wave inversions (TWI) is associated with the RV dilatation and dysfunction.[198,203,204] TWI in the left precordial leads reflects left ventricular involvement, suggesting that the extent of repolarization abnormalities on surface ECG correlates with the degree of structural changes.[5,198,201] Moreover, the extent of TWI on ECG may reflect the extent of RV scarring, as indirectly measured by electroanatomic voltage mapping in ARVC patients.[205, 206]

Table 3. The most common ECG findings in Arrhythmogenic Right Ventricular Cardiomyopathy

ECG findings in ARVC patients and relatives		
ECG Findings	**Frequency**	
	ARVC patients[5,6,46,196-201]	**Relatives**[22,122,123]
Repolarization ECG findings		
T-wave inversion V1-V3	35-87%	2-21%
T-wave inversion V1-V2	6-76%	1-9%
T-wave inversion left precordial leads	6-40%*	3%
T-wave inversion inferior leads	20-43%	Unknown
J-point elevation	Unknown	Unknown
Coved ST-segment elevation	Unknown	Unknown
Depolarization ECG findings		
Epsilon waves	9-33%	1-2%
TAD>55msec	18-95%	2-7%
Prolonged V1-V3 QRS duration (>110msec)	5-75%	Unknown
RBBB	6-12%	Unknown
iRBBB	3-29%	Unknown
Low voltage	Up to 33%	Unknown
QRS fragmentation	38-85%	Unknown
Late potentials in SAECG[#]	44-93%	35-74%

** 6-7% in cohorts with variant ARVC phenotypes, up to 40% in cohorts with left dominant arrhythmogenic cardiomyopathy*

[#] Refers to late potentials detected using Signal Averaged ECG. The lowest frequency reports in cohorts with mild ARVC and the highest frequency in cohorts with severe ARVC.

(ARVC: arrhythmogenic Right Ventricular Cardiomyopathy, ECG: electrocardiogram, left precordial leads: I, aVL, V5-V6, inferior leads: II, III, aVF, TAD: terminal activation duration, RBBB: right bundle branch block, iRBBB: incomplete right bundle branch block)

The elevation of the J-point, specifically in lateral and inferior leads, similar to that observed in early repolarization syndrome, has previously been reported in ARVC patients.[207] Coved ST segment elevation and pathologic reaction during an ajmaline test, similar to that noted in Brugada syndrome, has also been described.[208-210] Moreover, 16% of the patients in a previous study with typical Brugada ECG had RV wall motion and structural abnormalities corresponding to localized ARVC, while 8% fulfilled both the Brugada Syndrome and the ARVC diagnostic criteria.[211] All these findings suggest an overlapping between the Brugada Syndrome and ARVC electrocardiographic characteristics with still unknown clinical implications.

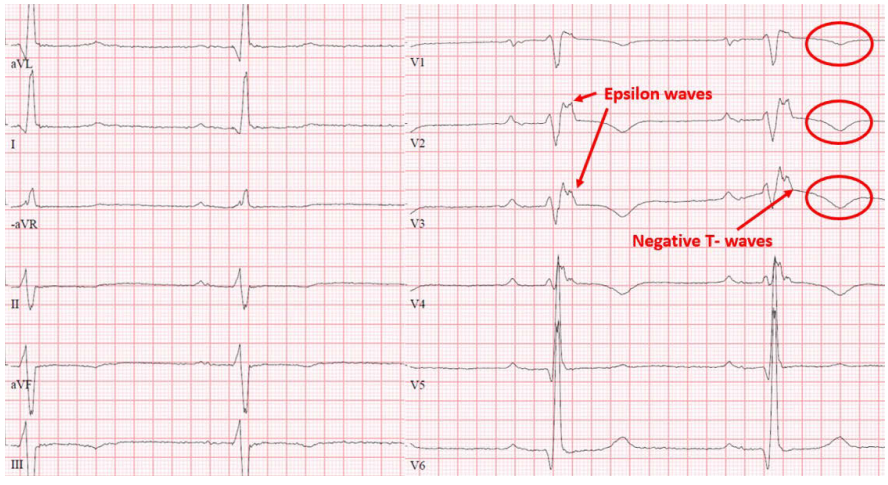

Figure 2. Example of ECG in an ARVC patient

The figure illustrates the ECG of a patient with ARVC. Note the negative T-waves in the right precordial leads V1-V3 and the epsilon waves at the end of the QRS complex.

4.3.2 Depolarization/ conduction abnormalities

The epsilon waves were described early in ARVC and are considered pathognomonic, indicating a major diagnostic criterion[2,19] (Figure 2). The definition of epsilon waves has evolved in the literature through the years.[19,26,27] The inconsistencies in the definition, the high interobserver variability reported, as well as the association of epsilon waves with a more severe stage of the disease raise questions as to its usefulness in ARVC diagnosis, particularly in the early stages, when other criteria are not fulfilled.[212,213]

A prolonged S-wave upstroke in the right precordial leads, also called *terminal activation duration* (TAD), has been proposed as a marker for ARVC.[19,196] A TAD >55msec is a common finding in ARVC cohorts and a minor diagnostic criterion.[195,196,198,214] A longer QRS duration in the right precordial leads (V1-V3) compared to lateral leads (V4-V6), complete right bundle branch block (RBBB), or incomplete right bundle branch block (iRBBB) are common ECG features that have been reported, but they are considered to be unspecific.[196-200] It has also been suggested in a recent study that the extent of the ECG depolarization abnormalities correlates to the extent of the conduction delay and scarring.[213]

Low voltage, in terms of decreased QRS amplitude, particularly in the right precordial leads, is commonly seen in advanced stages of the disease and is associated with RV dilatation.[215] Decreased QRS amplitudes have also been reported to predict a recurrence of arrhythmias in patients who have undergone ventricular tachycardia (VT) ablation.[216] Similarly, the fragmentation of

QRS complex has been reported in ARVC patients and is associated with arrhythmic events.[199,217,218] However, it is considered non-specific, as it can be seen in other scar-related cardiomyopathies, such as in ischemic cardiomyopathy.[219-221]

Late potentials recorded with SAECG reflect the delayed RV depolarization and are commonly encountered in ARVC.[222,223] Nonetheless, late potentials tend to appear in more severe stages of the disease, being a useful tool for follow-up rather than early diagnosis.[223-225] They are also unspecific, appearing in other scar-related diseases or even in healthy individuals, e.g., athletes.[222,226] In the last case, however, it has been reported a prolonged fQRS duration on the SAECG as the only pathologic finding, distinguishing these individuals from ARVC patients who usually have more extent pathology in SAECG.[227] The usefulness of late potentials has been questioned in the last few years, and it has been proposed to exclude them from the TFC.[228,229] Still, although unspecific, a careful evaluation and interpretation of SAECG together with other diagnostic examinations can contribute to the diagnosis of patients and relatives.[230]

4.4 Ventricular Arrhythmias

The evaluation of QRS morphology during ventricular tachycardias is very important for diagnosis.[19] A ventricular tachycardia with LBBB morphology and superior axis indicates an origin at the RV apex, which is a major diagnostic criterion.[2,19,28,197] In the case of ventricular arrhythmias from the outflow tract of the RV (RVOT), it can be difficult to differentiate between an idiopathic RVOT tachycardia from ARVC related ventricular tachycardias.

In a recent survey in Europe, 4.4% of the sustained ventricular tachycardias in ARVC have been reported having RBBB morphology, while in 3.1% of cases ventricular tachycardias with LBBB and RBBB morphology co-existed.[231] The prevalence of ventricular tachycardia with RBBB morphology was higher among patients with a pathogenic variant in the DSP gene, while the co-existence of ventricular tachycardias of LBBB and RBBB morphology was more prevalent among women.[231]

Several studies have been conducted in an attempt to find features that can differentiate between benign RVOT tachycardia and ARVC.[20,232,233] The QRS duration has been reported to be longer in most leads in ARVC compared to RVOT tachycardia. However, a QRS duration in lead I > 120msec, QRS notching in any lead, a QRS transition at V5 or further and the earliest onset of QRS in V1 have been suggested as more sensitive parameters.[232] Ventricular tachycardias with LBBB morphology and inferior axis, as well as frequent ventricular extrasystoles (>500 per 24 hours) perform as minor criteria for ARVC, according to the 2010 TFC; however, caution is required when these findings are observed in patients without a confirmed ARVC diagnosis.[19]

4.5 Family history/ genetics

The identification of a disease causing mutation in a patient with suspected ARVC is a major diagnostic criterion and can confirm the diagnosis.[19] This may be particularly useful in borderline cases and when a definite diagnosis is of importance and can lead to lifestyle changes, such as in competitive athletes. Unfortunately, the genetic screening can be negative in up to 70% of all ARVC cases.[53,234,235] Thus, a negative genetic test cannot preclude the diagnosis in a proband. The diagnosis in such cases should be based only on the clinical criteria.

4.6. Differential diagnosis and diagnostic challenges in ARVC

Although great advances have been made in the recognition and understanding of ARVC in the last decades, the diagnosis remains complex and challenging. The differential diagnosis, including RVOT tachycardia, athlete's heart, cardiac sarcoidosis, congenital heart diseases and other conditions leading to RV overload, can be difficult to rule out.[20,23,24,236] Myocarditis can be particularly difficult to differentiate, as these two entities share histopathologic characteristics and can present with similar clinical findings.[7] In cases of LV engagement or biventricular involvement, it is often impossible to differentiate from DCM.[5] Finally, several arrhythmogenic syndromes can present a phenotypic and genetic overlapping with ARVC, making an accurate diagnosis impossible.[35,71,85,208,209]

Table 4. The main differential diagnoses of Arrhythmogenic Right Ventricular Cardiomyopathy

Differential diagnoses of ARVC	
Condition	**Common characteristics with ARVC**
Electrical disorders	
Benign RVOT tachycardia	VA with origin from RVOT (LBBB morphology, inferior frontal plane axis)[20,236]
Brugada syndrome	Coved ST segment elevation, pathologic response to ajmaline test, VA, RV wall motion and structural abnormalities, mutations in SCN5A gene[84-86,208,209]
CPVT	Exercise induced VA, mutations in RYR-2 gene[35,71]
Conditions leading to RV overload	
Athlete's heart	T wave inversions, RV dilatation[24,237,238]
CHD (ASD, Uhl's anomaly, Epstein's anomaly)	RV dilatation and volume overload, fatty replacement of the myocardium (vid Uhl's anomaly)[239]
Pulmonary embolism/ PAH	RV dilatation and pressure overload, RV systolic dysfunction
Myocardial diseases	
Myocarditis	Inflammatory infiltrates in histopathologic examination, VA[7,104]
Cardiac sarcoidosis	Mimics ARVC with LV engagement: biventricular dilatation and dysfunction, ventricular arrhythmias[23]
Chaga's disease	Mimics ARVC with LV engagement: biventricular dilatation and dysfunction, VA, inflammatory infiltrates, fibrofatty replacement of the myocardium[240]
Neuromuscular Cardiomyopathies	Fatty infiltration of the myocardium in histopathologic examination[241]
DCM	Mimics ARVC with LV engagement: Negative T waves in inferior leads, low QRS amplitudes in limb leads, VA with LV origin, Biventricular dilatation[5,6]

ARVC: Arrhythmogenic Right Ventricular Cardiomyopathy, RVOT: Right ventricular right outflow tract, VA: ventricular arrhythmias, CPVT: Catecholaminergic Polymorphic Ventricular Tachycardia, LBBB: left bundle brunch block, RYR-2: ryanodine receptor 2, CHD: congenital heart disease, PAH: pulmonary artery embolism, RV: right ventricle, LV: left ventricle, ASD: atrial septum defect, DCM: dilated cardiomyopathy.

The most important differential diagnoses of ARVC are summarized on table 4.

The currently available diagnostic tests have limitations, and there is no single method that can confirm or preclude the diagnosis.[18,19,192] The resolution of cardiac imaging modules needs to be improved to enable early diagnosis.[18] The genetic screening can detect a disease-causing mutation in, maximum, 50% of the cases.[234,235] The low penetrance and slow progression of the

disease require extended and long follow-ups of all genetically predisposed individuals in order to detect early stages of ARVC.[21,22,122]

For all these reasons, ARVC diagnosis is still a challenge. More research and new diagnostic modalities are required to improve the diagnostic yield of the disease.

4.7 Novel diagnostic techniques– Electrocardiographic Imaging (ECGI)

ECGI is a new mapping technique for displaying electrophysiological data, based on the electrical data recorded from the torso.[242] The idea of recovering information about the regional intracardiac activity from the electrical signals recorded on the body surface, the so-called inverse problem of electrocardiography, has puzzled the scientific community for many decades.[243-246] Many experimental studies have been performed to develop inverse electrocardiographic solutions in order to create 3D models of the heart.[247-250] Early approaches modeled the heart as a combination of single fixed-location dipoles, moving dipoles, or multiple fixed-location dipoles.[247-249] More recent studies have developed algorithms for creating maps of the myocardial or isolated epicardial activation.[250,251] The latest approach has gained a lot of attention, resulting in the development of the modern ECGI systems.[247,251]

An ECGI system consists of a number of electrodes (50 to approximately 300, depending on the manufacturer) applied on the patient, either in strips or in a vest, and a mapping system which records the electrical signals[242] (Figure 3). In order to reconstruct the epicardial signals from the recorded body surface signals, the geometrical analogies of the torso are required. For that purpose, a CT-scan or MRI is performed while wearing the electrode strips or the vest, and a 3D image of the heart is recreated, displaying the electrodes in relation to the epicardium. Combining the location and electrical signals of the electrodes and applying the algorithm of the inverse solution, on which the system is based, 3D maps of the heart are reconstructed to display the epicardial potentials.[252-254]

The clinical applications of ECGI can be divided into three categories: atrial arrhythmias, cardiac resynchronization therapy (CRT), and ventricular arrhythmias. Several studies have shown the efficacy of ECGI in detecting the origin of the arrhythmia in atrial tachycardias, as well as in studying the mechanisms of atrial fibrillation, identifying new possible targets for catheter ablation.[255-260] Additionally, ECGI provides a better insight into the mechanisms of electrical dyssynchrony in heart failure, and great efforts have been made to identify new markers which could predict the patients' response to CRT

therapy.[261-265] Finally, ECGI has been effective in identifying the foci of ventricular tachycardias or ventricular extrasystoles, guiding the diagnosis and treatment during catheter ablation.[256,266-273]

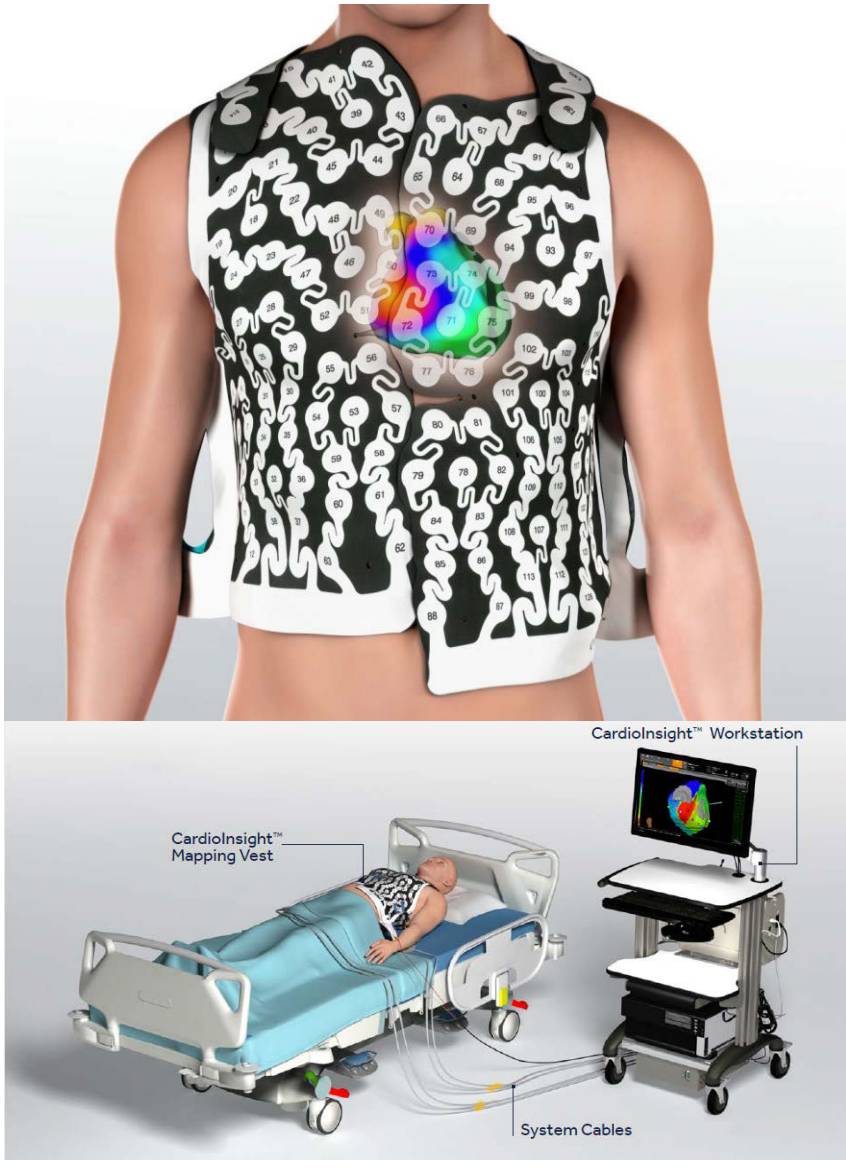

Figure 3. The ECGI system (CardioInsightTM)

The figure illustrates the main parts of an ECGI system, consisting of a 252-lead vest and a workstation. With the permission of Medtronic.

Over the last few years, new applications of ECGI have been proposed within the field of arrhythmogenic syndromes. In a study on 25 patients with genetically confirmed long QT syndrome (LQTS), the authors mapped the electrophysiological substrate for ventricular arrhythmias.[274] Despite some variability between the different types of LQTS, ECGI revealed areas with steep repolarization dispersion, and prolonged activation-recovery interval in all patients.[274] In a different study on 25 patients diagnosed with Brugada syndrome (BrS) and six controls with RBBB, ECGI demonstrated delayed activation, prolonged repolarization, and steep repolarization dispersion located on RVOT in BrS patients, but not in the controls.[275] In a more recent study on 32 BrS patients, ECGI revealed an impaired impulse conduction on RVOT after pacing or ajmaline administration, causing conduction delay, loss of local activation, and fractionation of the epicardial signals.[276] Similarly, in another study, an ajmaline test resulted in a prolonged activation time and decreased activation-recovery index on RVOT; both parameters were significantly higher among BrS patients with a history of sudden cardiac death.[277]

There are very few reports on the diagnostic efficacy of ECGI in patients with ARVC. In a case report in 2013, the authors reported for the first time the detection of fractionated signals and a lesion on LV, using ECGI.[278] A few years later, ECGI revealed a pathologic ventricular activation during sinus rhythm, areas with discontinued conduction, and fractionated electrograms in 20 ARVC patients in variable stages of the disease compared to the controls.[278,279] The areas where the electrophysiological abnormalities were located, correlated with scars detected using late gadolinium enhancement.[279] Moreover, there appeared to be repolarization abnormalities in the regions where the ventricular extrasystoles originated.[279]

These studies suggest a potential role of ECGI in the diagnosis of arrhythmogenic syndromes, such as ARVC and have been the inspiration for this doctoral project.

5. Management

5.1 Risk stratification for SCD

Once the diagnosis of ARVC has been confirmed, the most important role for the physician is the risk stratification of the patient for malignant arrhythmias and sudden cardiac death.[44] A timely implantation of an ICD as a primary prevention can be life-saving.[44]

The average risk for ventricular arrhythmias has been reported from 3.7%/year in cohorts with pathogenic variant carriers to 10.6%/year in cohorts with definite ARVC patients.[280] Several risk factors for arrhythmias have been proposed in previous studies.[21,281-283, 44,114,284]

A prediction model for ventricular arrhythmias in ARVC (risk calculator, www.arvcrisk.com) has been suggested in recent years, based on the following predictors: age, sex, cardiac syncope in the prior 6 months, non-sustained ventricular tachycardia, number of premature ventricular complexes in 24 h, number of leads with T-wave inversion, and right ventricular ejection fraction.[285] This model applies to all patients with ARVC without a history of ventricular arrhythmias and has been evaluated in several studies with good results.[237,286-288]

5.2 ICD therapy

In general, ICD is indicated in high-risk patients with a history of aborted SCD, hemodynamically unstable ventricular arrhythmias, or severe RV and/or LV heart failure.[17,127] ICD implantation for primary prevention in healthy gene carriers is not recommended.[127] The indications for ICD implantation in ARVC may, however, vary among countries due to socio-economic factors, the local healthcare system, and cost-benefit considerations.

Several studies have proven the effectiveness of ICD therapy in treating life-threatening arrhythmias, improving the long-term outcome. Appropriate ICD intervention has been reported in up to 78% of ARVC patients, depending on the cohort studied.[289-295] Multiple ICD discharges and VT storm are also not uncommon.

5.3 Pharmacological therapy and catheter ablation

The *pharmacological therapy* in ARVC consists of antiarrhythmic drugs (AAD), beta-blockers, and heart-failure drugs.[127] The AAD therapy is mainly symptomatic, aiming to improve the quality of life. The treatment choices are often made empirically, as randomized, prospective studies are not available.[127] Amiodarone is the only AAD that has been suggested to be effective in preventing symptomatic ventricular arrhythmias in ARVC.[296] However, an earlier study has shown that the majority of ARVC patients who experienced life-saving ICD therapy were already under AAD treatment, indicating that AAD probably have no effect on SCD prevention.[289] Even though there are no clinical studies proving the efficacy of beta-blockers in preventing ventricular arrhythmias and SCD in ARVC, beta-blockers are recommended in all ARVC patients, irrespective of whether a history of arrhythmias is present or not.[127,296] Treatment with angiotensin converting-enzyme (ACE) inhibitors, angiotensin II receptor (ATII) blockers, beta-blockers, and diuretics is recommended in all patients with a developed RV/ LV or biventricular heart failure.[127] Anticoagulation is only recommended as a secondary prophylaxis in patients with previously documented thrombosis.[127]

The role of *catheter ablation* in the treatment of ventricular arrhythmias has been explored even in early studies.[297] Several studies throughout the years have reported variable acute success and high recurrence rates after endocardial catheter ablation.[298-304] It has been hypothesized that this is because of the progressive nature of the disease as well as the epicardial lesions that are common in ARVC.[1,303] Studies on epicardial ablation or combined endocardial and epicardial approaches have shown better results, albeit a significant recurrence rate.[305-307] Accordingly, catheter ablation is considered a possible therapeutic strategy in ARVC patients with recurrent ventricular arrhythmias or frequent appropriate ICD interventions, despite maximal pharmacological therapy.[127] Moreover, it is considered a symptom relieving therapy rather that curative.

5.4 Lifestyle changes

Several studies have emphasized the role of exercise in the progression of ARVC phenotype.[52,110-114] The higher intensity and frequency of exercise have been associated with impaired biventricular systolic function.[111]Endurance exercise has been proven to increase the risk for ventricular arrhythmias and disease progression in ARVC patients and genotype-positive family members.[52,110,113,114] These results are consistent with earlier experimental studies on murine models of desmosomal mutations, which demonstrated that endurance exercise accelerates the disease progression.[115-117]

The restriction of the exercise load in ARVC patients and healthy gene carriers have been proven to lower the risk for ventricular arrhythmias and

SCD.[52,308,110] A recent study has shown that exercise during the last three years preceding a diagnosis was dose dependently associated with the risk of sustained ventricular arrhythmias, but only when it exceeded 15 to 30 METh (metabolic equivalent hours)/week.[309]

All these data support the restriction for all ARVC patients from competitive and/or endurance sports and athletic activities.[127,310] Leisure-time activities of high to moderate intensity should also be restricted.[127,310] These restrictions should apply to all patients with a definite, borderline, or possible ARVC diagnosis.[127,310] Recreational activities in low level may be allowed, depending on the clinical presentation.[127,310]

5.5 Screening, risk stratification, management, and follow-up of family members

Once a pathogenic mutation is identified in a proband, the genetic screening of family members is recommended in order to identify the individuals who are predisposed to developing the disease.[123,311,312] Repeated clinical evaluation is recommended for all gene carriers, every 1-3 years, particularly during adolescence and young adulthood, in order to ensure an early diagnosis.[17,123,127] The relatives who are not carriers of a known pathogenic variant do not need regular clinical evaluation, but they should be informed to seek medical care in case symptoms occur.[17] In the case where the genetic status of the proband is unknown, or when a disease-causing mutation is not identified, repeated lifelong clinical screening is recommended in first-degree relatives, as a late expression of the disease is not uncommon.[17,22,48,127] The clinical evaluation usually consists of a 12-lead ECG, echocardiography (or MRI depending on the local protocols and availability), 24 hours Holter monitoring, and exercise testing.[17,127]

Participation in competitive sports and recreational activities of moderate to high intensity is discouraged in all genotype-positive relatives, independent of the phenotype.[127,310] The same restrictions may be considered in relatives of ARVC patients with an unknown genotype.[127]

The risk stratification for relatives of ARVC patients is more complex. Previous studies suggest that family members have a lower arrhythmic risk compared to probands, probably because they are diagnosed in earlier stages of the disease.[291] Thus, an early diagnosis is the key to early management and a better outcome.

6. Aims of the doctoral project

The overall aim of this doctoral project was to explore the effectiveness of new technologies in detecting repolarization and depolarization disturbances in the early stages of ARVC and to emphasize the importance of early diagnosis.

- The aim of studies I, II, and IV was to explore the diagnostic capability of a new non-invasive mapping system (ECGI), which can record the body surface signals of the torso using 252 electrodes. More specifically, we aimed to explore whether repolarization abnormalities (**study I**) or depolarization abnormalities (**study II**) could be detected in ARVC patients and healthy genotype-positive phenotype-negative family members by the analysis of body surface signals recorded by ECGI. In **study IV**, we aimed to investigate whether ECGI could unmask abnormal activation patterns and delayed epicardial conductions in ARVC patients and in genotype-positive relatives by the analysis of the reconstructed epicardial signals.
- In **study III,** we aimed to describe the first Swedish cohort of SCD in the young due to ARVC and to identify parameters that were associated with a fatal outcome.

7. Methods

7.1 Patient selection

Studies I, II, and IV were conducted with the same study population. All subjects included were followed at the Molecular Inherited Cardiac Arrhythmogenic Syndromes Clinic, Cardiology Department, Uppsala University Hospital.

The study subjects were divided into three groups:

- **ARVC patients**, who fulfilled the 2010 Task Force Criteria[19] for definite ARVC diagnosis, regardless of genotype
- **M-carriers** (mutation carriers), who were genotype-positive phenotype-negative relatives of ARVC patients, i.e., they had been tested positive for a known family mutation in any desmosomal gene, but they had no arrhythmias or structural abnormalities on echocardiography and/or MRI, compatible with an ARVC diagnosis
- **Controls**, healthy relatives of ARVC patients, who had tested negative for a known family mutation in any desmosomal gene.

Inclusion criteria

1. Age 18-75 years old.
2. Proband or relative in a family with a definite ARVC diagnosis according to the revised Task Force Criteria 2010

Exclusion criteria

1. Known channelopathy, i.e. Long QT-syndrome or Brugada syndrome.
2. Other known cardiomyopathy or heart failure unrelated to ARVC.
3. Atrioventricular block type II or III, pacemaker dependency or complete bundle branch block at rest ECG.
4. History of myocardial infarction or heart surgery.
5. BMI > 31
6. Pregnancy

Study III was based on the Swedish **SUD**den Cardiac **D**eath of the **Y**oung study database (SUDDY), which includes 903 individuals, aged 0–35-years-old, who died of SCD in Sweden from January 1, 2000 to December 31, 2010.[14] All individuals who received a post-mortem ARVC diagnosis were identified and included in study III. For every case, five controls, matched by

sex, birth year, and home district, were drawn from the Register of the Total Population and Population Changes (n=110) and were included in the study.

7.2 Study design

7.2.1 Studies I, II, and IV

Studies I, II, and IV were based on a cross-sectional study (**BSM-detect ARVC study**) and were pre-defined sub-studies. All study subjects underwent a conventional diagnostic evaluation for ARVC consisting of a resting 12-lead ECG (inclusive the right precordial lead V4R), SAECG, 24-hour Holter monitoring, and 2-dimensional (D)-echocardiography with standardized RV projections and RV strain analysis.

The recording of the unipolar body surface potentials was performed with the CardioInsight non-invasive Electrocardiographic Mapping (ECM) System, software version 3.1, using a 252 electrode vest (CardioInsight^{TM}, Medtronic, MN). A non-ECG triggered CT scan with a low radiation protocol was performed just before or after the recording, in order to visualize the vest's electrodes in relation to the epicardium.

The study was performed in two steps:

- We first analyzed the body surface signals recorded by the body surface mapping (BSM) system, regarding repolarization abnormalities (**study I**) and depolarization abnormalities (**study II**). The analysis of the body surface signals was performed using the CardioInsight^{TM} non-invasive Electrocardiographic Mapping (ECM) System, software version 3.1. In both studies, the diagnostic capability of the system was compared with the conventional 12-lead ECG, aiming to compare the diagnostic effectiveness of these two techniques.
- We then analyzed the epicardial signals, reconstructed by the ECGI (**study IV**). For the offline analyses of the reconstructed epicardial signals, the commercial software was extended using a customized offline analysis tool in Matlab.

For the purpose of the study, from here on, we will use the term BSM System when referring to the recording and analysis of the body surface signals, and the term ECGI when referring to the reconstruction and analysis of the epicardial signals.

7.2.1.1 Study I

The evaluation of the body surface signals was qualitative, focusing on the polarity of the T-waves and the concordance with the QRS complex. A T-wave was characterized as positive, negative, biphasic, or isoelectric. The

QRS complex was characterized positive if the R wave amplitude was higher than the S wave, negative if the S wave was higher than the R wave, and balanced when both R and S waves had equal amplitudes. A T-wave was defined concordant when its polarity was the same with the QRS complex, discordant when the T-wave and QRS complex did not have the same polarity, and of inconclusive concordance when the QRS complex was balanced or when the T-wave was isoelectric or biphasic.

Each lead of the BSM vest was assigned a specific color related to the polarity and concordance of the T-wave, and repolarization maps were created. Each repolarization map was divided into four panels, related to the lead position on the chest: right front (rightF), right back (rightB), left front (leftF), and left back (leftB) panels (Figure 4).

The repolarization maps of the ARVC patients and controls were visually evaluated in order to define the different repolarization patterns. The repolarization maps of M-carriers were characterized as pathologic or normal, based on the patterns recognized in the ARVC group and the controls.

In each repolarization map, the number of leads with negative, positive, isoelectric, and biphasic T waves, as well as the number of leads with negative concordant, positive disconcordant, positive concordant, and positive discordant T waves, were calculated. A repolarization index was then introduced, based on the number of leads with a specific T-wave polarity and T-QRS concordance, in order to discriminate a normal repolarization pattern from a pathologic one objectively.

7.2.1.2 Study II

In this study, we focused on the QRS dispersion, calculated by the BSM vest (BSM-QRS dispersion), compared with the QRS dispersion, calculated using a 12-lead ECG (ECG-QRS dispersion).

Calculation of the ECG-QRS dispersion: The QRS duration in each lead of the surface ECG was manually measured with digital calipers, from the beginning of the QRS complex to its end and calculated as the mean value of three consecutive complexes. The ECG-QRS dispersion was defined as the difference between the minimum and maximum mean QRS duration, and was considered pathologic when >40msec, in accordance with previous reports.[313,314]

Calculation of the BSM-QRS dispersion: Three beats for each participant were randomly selected and exported from the BSM system to the MATLAB software (MATLAB version R2019b, MathWorks, Natick, MA, USA) for a manual analysis. The QRS duration was measured with electronic calipers, starting from the beginning of the QRS complex to its end. The mean value of the three QRS durations per lead was calculated. The localization of the minimum and maximum mean QRS durations was reported for comparison. The BSM-QRS dispersion was defined as the difference between the minimum

and the maximum mean QRS duration and was considered pathologic when >40msec, corresponding to the definition of the ECG-QRS dispersion.

Localization of the minimum and maximum QRS duration in the 12-lead ECG and BSM recordings: The ECG leads were grouped into four different anatomical groups: right precordial (V1-V3), left precordial (V4-V6), lateral (I, aVL, aVR), and inferior leads (II, III, aVF) in order to report the localization of the minimum (shortest) and maximum (longest) QRS duration. In the BSM recordings, the location of the minimum and maximum QRS durations was the panels where the leads with the ten minimum and maximum values, respectively, were located.

7.2.1.3 Study IV

In study IV, we proceeded with the analyses of the reconstructed epicardial signals. The analysis was performed in two steps: the evaluation of the epicardial activation in both ventricles and the evaluation of the RV epicardial activation alone.

Evaluation of the epicardial ventricular activation:

Three random beats per participant were selected and averaged automatically by the system, with at least 200 similar beats, for noise reduction. For each averaged beat, an activation map was created for offline analysis using a customized offline analysis tool in Matlab.

The local epicardial activation, automatically annotated by the system, was defined as the point of the last negative dV/dt of the local electrogram before the T-wave. The earliest and latest epicardial activations were defined by the segments of the ventricles, where the first or latest local epicardial activation was noted. The time from the earliest to the latest local epicardial activation was defined as the total activation time (tVAT). In order to identify areas with conduction delay, we further focused on the last 20 msec of the total activation time (terminal ventricular activation, $VAte_{20}$). The regions of the ventricles activated during the $VAte_{20}$ were reported, and the epicardial surface they covered was defined as the terminal activation area ($aVAte_{20}$). The tVAT, $aVAte_{20}$, as well as the mean time required for the activation of all regions within the terminal activation area ($TaVAte_{20}$) were automatically calculated by the system and compared between the study groups.

Evaluation of the RV epicardial activation:

For this analysis, the Activation Time Editing tool of the Cardionsight system, software version 3.1, was used. Multiple electrograms were chosen and displayed simultaneously on the activation map, and the earliest and latest local activation were identified. The time from the earliest to the latest local activation was defined as the activation time and was calculated for the whole RV (RVAT) and separately for the RV anterior wall (RVAT-AW) and for the RV

inferior wall (RVAT-IW). The sites of the earliest and latest local activation were reported.

The epicardial signals were categorized as rS, Rs, rSr', qRs, or qR, depending on their morphology. The T waves were defined as positive, negative, isoelectric, or biphasic.

7.2.2 Study III

Study III was a pre-defined sub-study of the SUDDY study. For all cases and controls, clinical and sociodemographic data from the National Patient Registry (NPR), the Cause of Death Registry, and the Longitudinal integrated database for health insurance and labor market studies (LISA) were retrieved and analyzed. Medical records (MRs) from the hospital patient visits during the last six months before death were retrieved for all cases. The autopsy reports from the forensic and clinical autopsies were collected from the Swedish Board of Forensic Medicine and Hospital Clinical Pathology departments, respectively. A standardized interview, including a three-generation family history, was performed over the phone with a close relative.

Hospital visits and ICD-10 codes (International Statistical Classification of Diseases and Related Health Problems (ICD) version 10) related to the cardiovascular systems (ICD-10:R00-R09, R55, R56, I42-I43, I44-I49, I30-41, I50-52), registered in the NPR six months before the death date, were compared between the cases and controls.

Past medical history and symptoms prior to death were retrieved from the MRs and family interviews. Electrocardiograms (ECGs) were collected from the medical records and pre-military conscription examination. The reports from the echocardiography, cardiac MRI, and 24-hour ECG recordings were collected and revised. Relevant family history, including family history of SCD, cardiomyopathy or other arrhythmogenic syndrome, or Implantable Cardioverter Defibrillator (ICD) was retrieved from a three generation pedigree obtained during the interviews and from MRs. Anatomic and histopathological findings, information on time, and circumstances of death were extracted from the autopsy reports and the family interviews. Information on intensity and frequency of physical activity and previous participation in sports were retrieved from MRs and family interviews.

7.3 Statistical analysis

The data were analyzed using IBM Statistical Package for the Social Sciences, version 26-28 for Windows, (IBM Corp., IBM SPSS Statistics for Windows, Armonk, NY) and R, version 4.0, 2020 (www.R-project.org).

The following statistical methods were used:

- **Kruskal- Wallis** and **Mann-Whitney** U-test were performed in order to investigate the differences between the groups (Studies I–IV).
- **Conditional logistic regression** was performed for comparison between the cases and the controls (Study III).
- **Logistic regression analysis** was performed on the best predictor variables in order to determine an equation for the calculation of the logarithm of the odds, which was defined as the repolarization index (Study I).
- A **Receiver Operating Characteristic (ROC) analysis** was performed on the ARVC patients and controls in order to evaluate the diagnostic capacity of ECG-QRS dispersion, BSM-QRS dispersion, terminal activation area, total activation time, and RV activation time. A cut-off was identified for each of above-mentioned parameters with the best possible specificity and sensitivity (Studies II and IV).

8. Results

8.1 The diagnostic capability of ECGI in ARVC diagnosis– cohort characteristics (Studies I, II, and IV)

In total, 12 ARVC patients, 8 controls, and 20 M-carriers were enrolled in the study. The demographic and baseline clinical findings of conventional diagnostic tests are presented in Table 5.

Table 5. Baseline clinical characteristics of the study populations

	Controls (n=8)	ARVC patients (n=12)	M-carriers (n=20)
Sex, males	5 (62.5)	8 (67)	8 (40)
Age, years, mean (SD)	39 (18)	50 (16)	44 (14)
Gene mutations	0 (0)	10 (83)	20 (100)
plakophillin-2		7 (58)	10 (50)
desmoplakin		1 (8)	4 (20)
desmoglein-2		2 (16)	3 (15)
desmocollin-2		0	3 (15)
Clinical events / Arrhythmias			
Cardiac syncope	0	3 (25)	0
Aborted SCD	0	1 (8)	0
Non-sustained VT	0	4 (33)	0
Sustained VT	0	6 (50)	0
≥500 VES/ 24 hours	0	8 (67)	0
ICD	0	10 (83)	0
Antiarrhythmic drugs	0	4 (33)	0
Prior VT ablation	0	1 (8)	0
12 lead ECG			
Heat rate, bpm (mean ±SD)	61 (9)	56 (9)	64 (9)
Repolarization abnormalities*:	0	12 (100)	2 (10)
T wave inversion V1-V3 or beyond	0	10 (83)	2 (10)
T wave inversion III and aVF	0	7 (58)	0
T wave inversion V5-V6	0	4 (33)	0
T wave inversion V4R	4 (50)	10 (83)	11 (55)
Depolarization abnormalities*:	0	9 (75)	2 (10)
Prolonged TAD in V1, V2, or V3	0	8 (67)	2 (10)
Epsilon waves	0	6 (50)	0
Signal Averaged ECG			
Late potentials (1-3 criteria)	2 (25)	11 (92)	5 (25)
FQRSd, msec (mean ±SD)	107 (8)	153 (27)	110 (16)
Echocardiographic examination			
RV WMA	0	8 (67)	0
RVOT – PLAX (mm/m2), mean ±SD	1.6 (0.2)	1.9 (0.3)	1.5 (0.2)
– PSAX (mm/m2), mean ±SD	1.7 (0.2)	2.0 (0.2)	1.6 (0.3)
RV-FAC <40%	0	11 (92)	0
LV-EF % (mean ±SD)	62 (4)	63 (4)	61 (4)

Figures are numbers with percentages in brackets unless otherwise stated.
*(n= number of study subjects; SCD= Sudden Cardiac Death; SD= standard deviation; VT= Ventricular Tachycardias; VES= Ventricular Extrasystoles; ICD= Implantable Cardioverter Defibrillator; RV= right ventricle; WMA= wall motion abnormalities; RVOT= right ventricular outflow tract; PLAX /PSAX= parasternal long/short axis; RV-FAC: right ventricular–fractional area change; LVEF= left ventricular ejection fraction; TAD= Terminal Activation Duration; *Figures denote any of the respective ECG abnormalities)*

8.2 Repolarization abnormalities revealed by the body surface potentials (Study I)

8.2.1 BSM repolarization maps and patterns in the ARVC patients and the controls

The initial evaluation of the repolarization maps of the ARVC patients and controls revealed three different repolarization patterns.

Repolarization pattern 1 presented negative concordant T-waves in the whole rightF and rightB panels. The leftF panel presented negative concordant T-waves in the upper half, which gradually changed to positive disconcordant T-waves in the middle, and finally to positive concordant T-waves at the bottom. The leftB panel showed a greater non-consistent diversity in the polarity and concordance of the T-waves (Figure 4a).

Repolarization pattern 2 presented the same pattern in both the RightF and RightB panels, with negative, concordant T-waves. However, the positive disconcordant T waves in the leftF panel, observed in the repolarization pattern 1, had disappeared (Figure 4b). The leftB panel here also presented a greater variation in the polarity and concordance of the T-waves.

Repolarization pattern 3 presented a high variation on the polarity and concordance of the T-waves and differed from the repolarization patterns 1 and 2 in all four panels (Figure 4c).

All eight controls and none of the ARVC patients appeared to have the same repolarization pattern 1, which was therefore considered and defined as the normal repolarization pattern. The repolarization patterns 2 and 3 were present in all the ARVC patients but in no controls and were therefore defined as pathologic. Three ARVC patients presented the repolarization pattern 2 and nine the repolarization pattern 3. Both of the ARVC patients without negative T-waves in the right precordial leads V1-V3 on the 12-lead ECG had a repolarization pattern 3 on their repolarization maps.

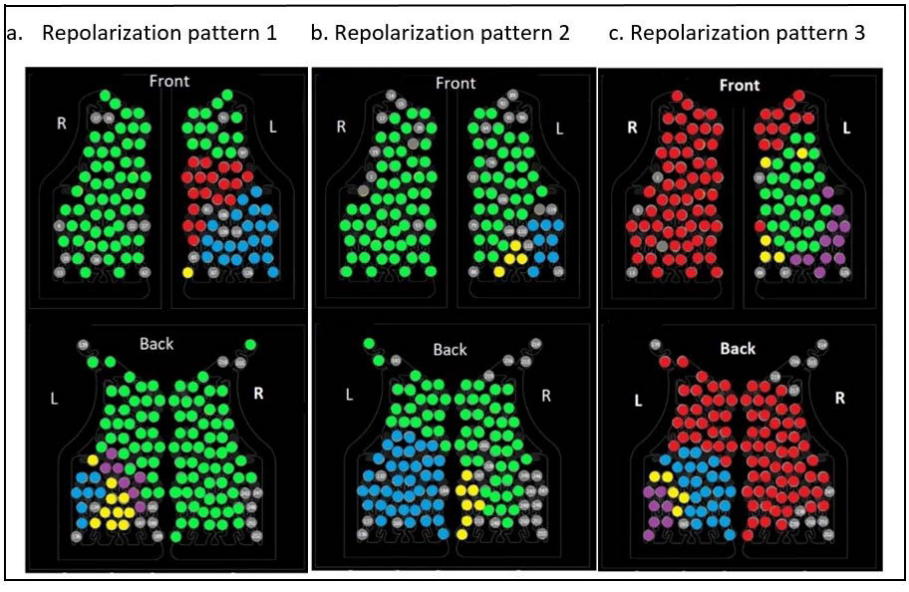

Figure 4. Examples of the three repolarization patterns in ARVC patients and controls

The figure illustrates the repolarization maps on the front and the back of the chest in one control (a) and two ARVC patients (b and c). Note the normal repolarization pattern 1 (a) on the control and the two different patterns, pattern 2 (b) and pattern 3 (c), observed in the ARVC patients.
(R= right; L= left; green= negative concordant T waves; red= positive discordant; blue= positive concordant; purple= negative disconcordant T waves; yellow= isoelectric or biphasic T waves, or inconclusive concordance; grey= none or too noisy signals)

8.2.2 BSM repolarization maps and patterns in the M-carriers

The majority of the M-carriers (15/20) presented a normal repolarization pattern 1 (Figure 5.a). None of them had pathologic negative T-waves on the right precordial leads. Four of the five remaining study subjects presented a repolarization pattern 2 (Figure 5.b) and one a repolarization pattern 3 (Figure 5.c). One individual with a repolarization pattern 2 and the only M-carrier with repolarization pattern 3 had negative T-waves on the right precordial leads at a resting 12-lead ECG. The remaining three subjects with pathologic repolarization patterns had no repolarization abnormalities on a resting ECG.

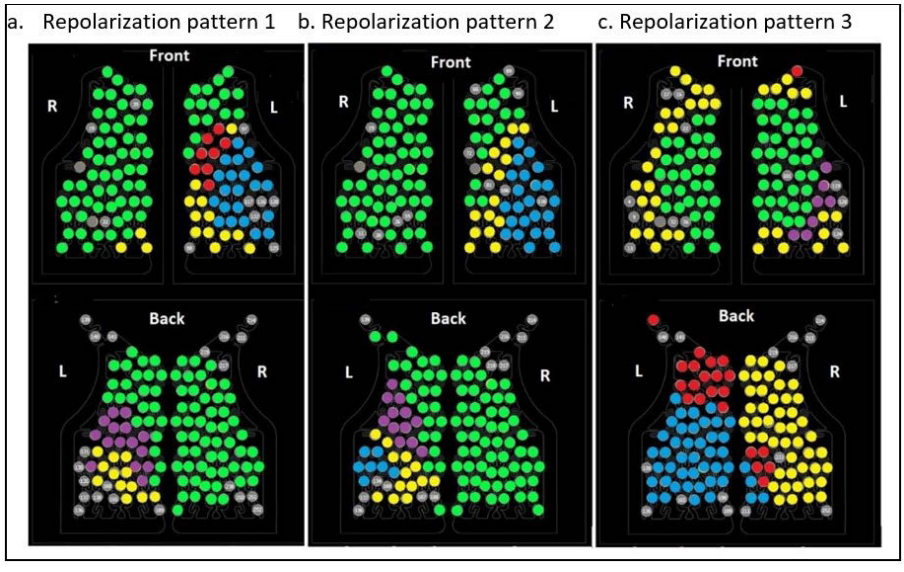

Figure 5. Examples of repolarization patterns recorded in three M-carriers

The figure illustrates the different repolarization patterns encountered in M-carriers. Same abbreviations as in figure 4.

8.2.3 Repolarization Index

The best predictor variables for the classification of the repolarization patterns were the positive T-waves at the leftF panel (Positive leftF) and the positive disconcordant T-waves at the leftF panel (PosDisconcordant leftF). As all repolarization maps were created based on both the polarity and concordance of the T waves, we chose to use the variable PosDisconcordant leftF for the further analysis. Indeed, the absence of the positive disconcordant T waves at the leftF panel was the first change noted between the repolarization patterns 1 and 2. Moreover, as the negative concordant T waves on both the right panels were consistent in both repolarization patterns 1 and 2 but disappeared in the most pathologic pattern 3, we chose to use this variable (NegConcordant rightF +rightB), too.

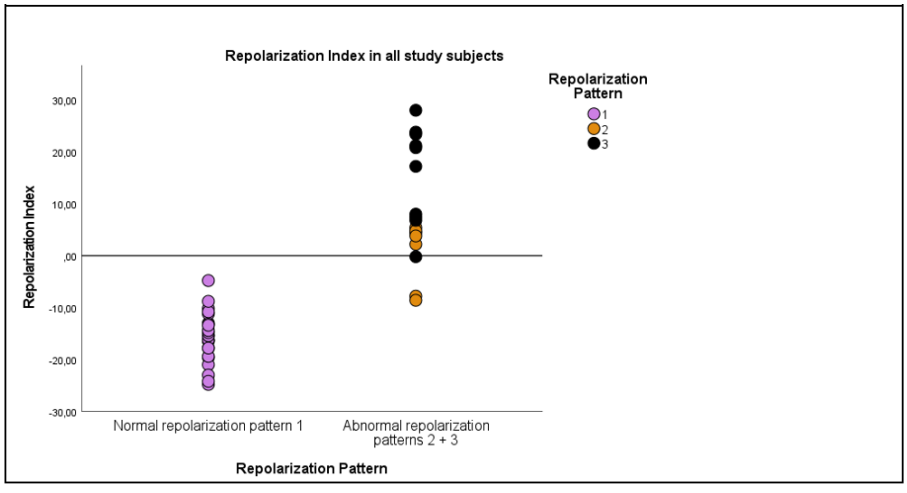

Figure 6. The repolarization index per repolarization pattern

The figure shows the repolarization index for each repolarization pattern. Note that a positive repolarization index indicates an abnormal repolarization pattern 2 or 3, and a negative one indicates a normal repolarization pattern 1. Adapted from "Repolarisation abnormalities unmasked with a 252-lead BSM system in patients with ARVC and healthy Gene Carriers.", V. Kommata, 2022, PACE.

A **logistic regression analysis** was performed using the variables *NegConcordant rightF +rightB* and *PosDisconcordant leftF*. The repolarization index was calculated by applying the following equation:

Repolarization index= 28- 0.2 x (NegConcordant rightF +rightB) –0.6 x (PosDisconcordant leftF)

A cut-off zero could be used to discriminate a normal repolarization pattern 1 (negative values) from the pathologic repolarization patterns 2 and 3 (positive values). The repolarization index for all the study subjects is shown in Figure 6. Specifically, 23/23 subjects with a normal repolarization pattern and 15/17 with pathologic repolarization patterns were classified correctly using the repolarization index.

8.3 Depolarization changes / QRS dispersion evaluated using Body Surface Mapping (Study II)

8.3.1 QRS durations and dispersion calculated from the BSM recordings

The minimum QRS duration (QRS d min) was similar in all study groups. However, the maximum (QRS d max), the mean QRS duration (QRS d mean), and the SD (QRS d SD) were significantly higher in the ARVC patients compared to the controls and M-carriers (Table 6). The BSM-QRS dispersion was significantly higher in the ARVC patients.

Table 6. QRS durations and dispersions calculated from the BSM recordings.

	Controls (n=8)	ARVC patients (n=12)	M-carriers (n=20)	p-values
BSM recordings				
QRS d mean	84 (10)	104 (15)	84 (8)	<0.05
QRS d min	69 (9)	67 (8)	64 (10)	0.504
QRS d max	98 (11)	132 (19)	99 (9)	<0.05
QRS d SD	6 (1)	14 (4)	8 (2)	<0.05
BSM-QRS dispersion	29 (7)	65 (17)	35 (6)	<0.05
BSM-QRS disp LF panel	26 (7)	57 (21)	31 (7)	<0.05
BSM-QRS disp RF panel	20 (8)	44 (21)	25 (8)	<0.05
BSM-QRS disp LB panel	19 (4)	34 (20)	23 (7)	<0.05
BSM-QRS disp RB panel	13 (4)	25 (22)	14 (6)	0.741

The figures are mean QRS duration in milliseconds with one standard deviation in brackets, unless otherwise stated. (disp= dispersion; d= duration; n= number of study subjects; SD= standard deviation, min= minimum value, max= maximum value, LF= front left panel, RF= front right panel, LB= back left panel, RB= back right panel). Adopted from "QRS dispersion detected in ARVC patients and healthy gene carriers using 252-leads Body Surface Mapping - an explorative study of a potential diagnostic tool for Arrhythmogenic Right Ventricular Cardiomyopathy." V. Kommata, 2021, PACE.

8.3.2 QRS durations and dispersion calculated from a resting 12-lead ECG

The minimum (QRS d min) and maximum (QRS d max) QRS durations, measured manually, were significantly higher in the ARVC patients compared

to the controls and M-carriers, although the automatically calculated QRS duration (QRS d mean) was the same in the three study groups. The SD of all QRS durations (QRS d SD) was also significantly higher in the ARVC group, revealing a higher distribution (Table 7). The ECG-QRS dispersion was significantly higher in the ARVC patients compared to the other two groups.

Table 7. QRS durations and dispersion calculated from a 12-lead ECG.

	Controls (n=8)	ARVC patients (n=12)	M-carriers (n=20)	p-values
12-lead ECG				
QRS d mean	89 (12)	98 (18)	89 (9)	0.376
QRS d min	71 (7)	82 (15)	67 (6)	<0.05
QRS d max	97 (7)	123 (18)	97 (10)	<0.05
QRS d SD	8 (3)	13 (5)	9 (2)	<0.05
QRS d V4R	80 (6)	105 (16)	79 (11)	<0.05
QRS d V1-V3	91 (8)	111 (19)	90 (10)	0.050
QRS d V4-V6	86 (10)	100 (22)	80 (8)	<0.05
QRS d I, aVL, aVR	78 (7)	91 (18)	75 (6)	<0.05
QRS d II, III, aVF	84 (11)	99 (16)	77 (7)	<0.05
ECG-QRS dispersion	25 (8)	42 (15)	29 (7)	<0.05

The figures are mean QRS duration in milliseconds with one standard deviation in brackets. (d= duration; n= number of study subjects; SD= standard deviation, min= minimum value, max= maximum value). Adopted from "QRS dispersion detected in ARVC patients and healthy gene carriers using 252-leads Body Surface Mapping - an explorative study of a potential diagnostic tool for Arrhythmogenic Right Ventricular Cardiomyopathy." V. Kommata, 2021, PACE.

8.3.3 Localization of the minimum and maximum QRS duration in a 12-lead ECG and BSM recordings

On ECG recordings, almost all controls (7/8) and ARVC patients (11/12) presented the longest QRS durations in the right precordial leads V1-V3 (Tables 8 and 9). The one control who differed appeared the longest QRS in the inferior leads, while the one ARVC patient who differed had a maximum QRS duration in the lateral leads. The shortest QRS durations, on the other hand, were most commonly located in the lateral leads, followed by the inferior leads in both groups. The minimum and maximum QRS durations in the M-carriers appeared to be of similar localization.

In BSM recordings, the localization of minimum and maximum QRS durations was more variable (Tables 8 and 9). The longest QRS durations were found in the left front panel of the vest in 7/12 ARVC patients and 3/8 controls, to the right front panel in 5/12 ARVC patients and 3/8 controls, and to the left back panel in two more cases in each group. The shortest QRS durations were more commonly located on the left front panel (in 6/12 ARVC patients and 4/8 controls), followed by the right front panel (in 3/12 ARVC patients and 2/8 controls), and the left back panel (in 2/12 ARVC patients and 2/8 controls). The M-carriers also presented with variable localization of the minimum and maximum QRS durations.

Table 8. The location of the longest and shortest QRS duration in individual controls assessed by a 12-lead ECG and 252-lead BSM recordings.

	Longest and shortest QRS in the BSM recordings				Longest and shortest QRS in a 12-lead ECG			
ID	RFpanel	LFpanel	LBpanel	RBpanel	V1-V3	V4-V6	aVL, I, aVR	II, III, aVF
C1								
C2								
C3								
C4								
C5								
C6								
C7								
C8								

The location with the longest QRS duration is marked with blue and the location with shortest QRS duration with grey. Adopted from "QRS dispersion detected in ARVC patients and healthy gene carriers using 252-leads Body Surface Mapping - an explorative study of a potential diagnostic tool for Arrhythmogenic Right Ventricular Cardiomyopathy." V. Kommata, 2021, PACE.

Table 9. The location of the longest and shortest QRS durations in individual ARVC patients assessed by a 12-lead ECG and 252-lead BSM recordings.

	Longest and shortest QRS in the BSM recordings				Longest and shortest QRS in a 12-lead ECG			
ID	RFpanel	LFpanel	LBpanel	RBpanel	V1-V3	V4-V6	aVL, I, aVR	II, III, aVF
P1								
P2								
P3								
P4								
P5								
P6								
P7								
P8								
P9								
P10								
P11								
P12								

The location with the longest QRS duration is marked with blue and the location with shortest QRS duration with grey. Adopted from "QRS dispersion detected in ARVC patients and healthy gene carriers using 252-leads Body Surface Mapping - an explorative study of a potential diagnostic tool for Arrhythmogenic Right Ventricular Cardiomyopathy." V. Kommata, 2021, PACE.

8.3.4 Correlation between the ECG-QRS dispersion and the BSM-QRS dispersion

All controls had a normal ECG-QRS dispersion (≤40msec), but only 5/12 ARVC patients had an ECG-QRS dispersion >40msec; the ECG-QRS dispersion could, thus, only detect a minority of ARVC patients. The BSM-QRS dispersion was abnormal (i.e., >40msec) in all but one ARVC patient, but it was normal in all but one of the controls. When comparing the ECG-QRS dispersion with the BSM-QRS dispersion (Figure 7), 6/7 ARVC patients with a normal ECG-QRS dispersion had a BSM-QRS dispersion >40msec (Figure 7).

ROC analysis confirmed the above results. The cut-off 40msec had a sensitivity of 60% and 100% specificity for ECG-QRS dispersion and 92% sensitivity and >90% specificity for the BSM-QRS dispersion.

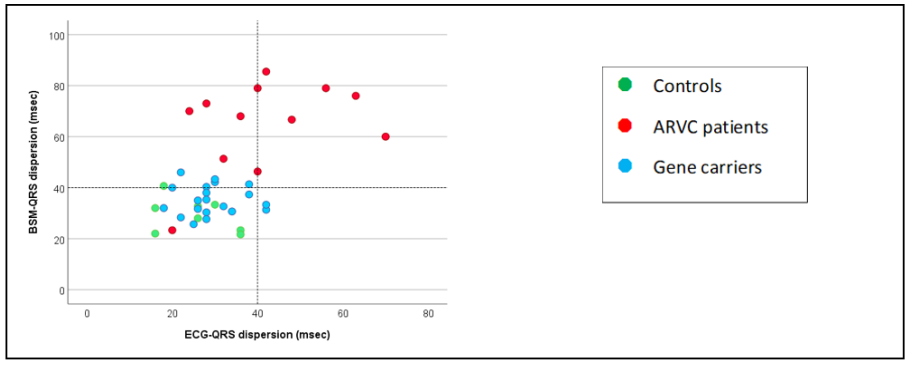

Figure 7. The BSM-QRS dispersion and ECG-QRS dispersion in all study groups

Adopted from "QRS dispersion detected in ARVC patients and healthy gene carriers using 252-leads Body Surface Mapping - an explorative study of a potential diagnostic tool for Arrhythmogenic Right Ventricular Cardiomyopathy." V. Kommata, 2021, PACE.

The majority of the M-carriers (18/20) revealed a normal ECG-QRS dispersion. The two individuals with abnormal ECG-QRS dispersion had a slightly elevated dispersion of 42msec and a TAD>55msec, but their BSM-QRS dispersion was normal. The majority of the M-carriers (16/20) had a normal BSM-QRS dispersion, too. However, four of them had abnormal BSM-QRS dispersions, ranging between 41 and 46 msec, although the ECG-QRS dispersion was normal. These individuals did not fulfil any depolarization or repolarization criteria for ARVC on surface ECG or SAECG.

8.4 Epicardial ventricular activation evaluated using Electrocardiographic Imaging (Study IV)

8.4.1 Terminal epicardial ventricular activation

The terminal ventricular activation ($VAte_{20}$) occurred in an area, including the RVOT and the cardiac base in all controls. The basal segment of the LV was always involved during the $VAte_{20}$. Furthermore, in most controls (5/8), even the basal segment of the RV was involved (Figure 8). In three controls, parts of the LV apex and/or LV lateral wall were also activated during the last 20msec.

All of the ARVC patients had a different pattern of $VAte_{20}$. RVOT was still one of the last segments activated, but no parts of the LV were activated during the last 20msec. The $VAte_{20}$ involved different parts of the RV: RVOT (in 8/12 cases), RV posterior wall (in 5/12 cases), RVIW (in 3/12 cases), RV apex (in 2/12 cases), and RV free wall (in 1/12 cases) (Figure 8).

The area activated during the terminal ventricular activation ($aVAte_{20}$) was significantly smaller in the ARVC group compared to the controls (35 cm^2 vs 87 cm^2, $p<0.05$). The tVAT and $TaVAte_{20}$ were both longer (99 msec vs. 58 msec, $p<0.05$; 92 msec vs. 49 msec, $p<0.05$).

The M-carriers presented variable patterns of $VAte_{20}$. Half of the M-carriers (10/20) presented normal $VAte_{20}$, similar to the controls, involving RVOT and LV base (+/- RV base, LV lateral wall, or LV apex) (Figure 8). Nine M-carriers presented $VAte_{20}$ at RVOT and LV base (+/- RV base), as in the controls, but also in additional areas of the RV (Figure 8). The additional RV segments involved in the terminal ventricular activation were: RV inferior wall (in 6/20 cases), RV posterior wall (in 1/20 cases), RV apex (in 1/20 cases), and RV free wall (in 1/20 cases). One last M-carrier presented terminal ventricular activation only at RVOT and RV inferior wall; in this case, the LV base was activated earlier (Figure 8).

In M-carriers, the $aVAte_{20}$ was larger compared to the ARVC patients (70 cm^2 vs. 35 cm^2, $p<0.05$) and was similar to the controls. In contrast, the tVAT and $TaVAte_{20}$ were shorter compared to the ARVC group (63 cm^2 vs. 99 cm^2, $p<0.05$; 52 cm^2 vs. 92 cm^2, $p<0.05$). Remarkably, when dividing the M-carriers into two sub-groups, those with similar $VAte_{20}$ as in the controls and those with additional or different areas of $VAte_{20}$, the last sub-group presented significantly smaller $aVAte_{20}$ compared to the first sub-group (53cm^2 vs. 87cm^2, $p<0.05$) and similar to ARVC patients. The tVAT and $TaVAte_{20}$ were comparable in the two sub-groups (65msec vs. 60msec, $p=0.529$, 54msec vs. 50msec, $p=0.579$).

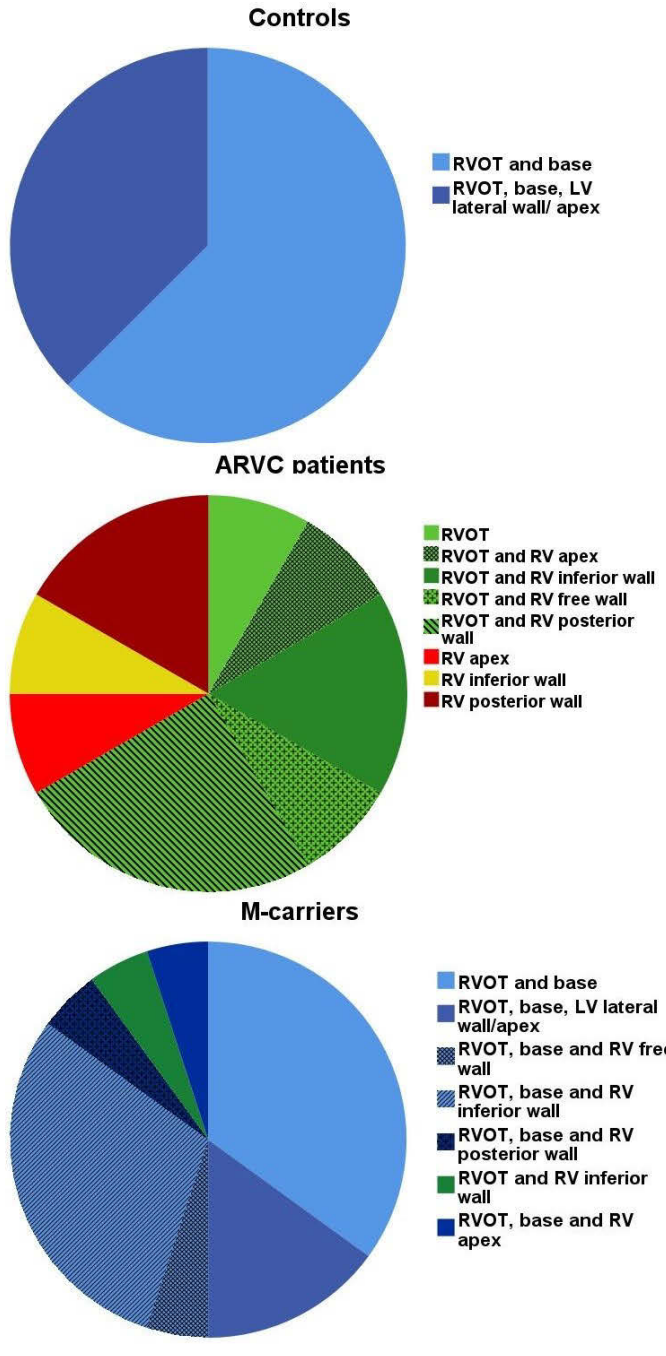

Figure 8. The location of the terminal ventricular activation

The figure illustrates the distribution of the terminal ventricular activation in the three study groups.

8.4.2 RV epicardial activation

Almost all controls (6/8) had the earliest RV epicardial activation at the RV paraseptal region and the latest activation at the RVOT (Table 10).

In the ARVC group, the location of the earliest and latest RV epicardial activations presented a larger heterogeneity, even if it did not differ statistically from the controls. Only 5/12 ARVC patients had the earliest activation at the RV paraseptal region and last at the RVOT, like the controls. Most of them (7/12) presented different earliest activations, latest activation, or both (Table 10).

Similarly, the M-carriers presented a higher variability regarding the pattern of the RV epicardial activation. In only 8/20 subjects, the activation pattern was similar to the controls, with the earliest activation at the RV paraseptal region and the latest at the RVOT.

As shown in Table 10, the ARVC patients presented a significantly longer RVAT and RVAT-IW compared with the controls and the M-carriers.

Table 10. Characteristics of the RV epicardial activation

	Controls (n=8)	ARVC patients (n=12)	M-carriers (n=20)	p-values
Earliest activation whole RV				0.703
Earliest activation RVAW				
paraseptal	87.5	66.7	65.0	
base RVAW	0	8.3	15.0	
free wall	0	8.3	10.0	
Earliest activation RVIW				
apical segment IW	12.5	8.3	0	
basal segment IW	0	8.3	10.0	
Latest activation whole RV				0.500
Latest activation RVAW				
RVOT	87.5	66.7	70.0	
Base RVAW	0	8.3	0	
Latest activation RVIW				
basal segment IW	12.5	25.0	30.0	
Activation time (msec), mean (SD)				
RVAT	43 (7)	66 (18)	51 (9)	<0.05
RVAT-AW	43 (6)	57 (17)	49 (8)	0.073
RVAT-IW	35 (8)	47 (18)	31 (12)	<0.05

The figures represent numbers with percentages in brackets, unless otherwise stated. The p-values refer to the comparison between the three groups with Kruskal-Wallis test. RV: right ventricle, AW: anterior wall, IW: inferior wall, RVOT: right ventricle outflow tract, AT: activation time

When dividing the M-carriers into two sub-groups depending on their terminal ventricular activation pattern, those with a deviating pattern (involving parts of the RV other than RVOT) had a longer RVAT (55msec vs. 48msec, p=0.43).

8.4.3 The diagnostic efficacy of terminal ventricular activation area ($aVAte_{20}$), total ventricular activation time (tVAT), and RV activation time (RVAT)

ROC analysis revealed that $aVAte_{20}$ of <68 cm^2 could identify the ARVC patients with 83% sensitivity and 87.5% specificity (Figure 9.a). A tVAT of >76 msec had 83% sensitivity and 100% specificity (Figure 9.b). Similarly, a RVAT of >49 msec could detect the ARVC patients with 83% sensitivity and 87.5% specificity (Figure 9.b).

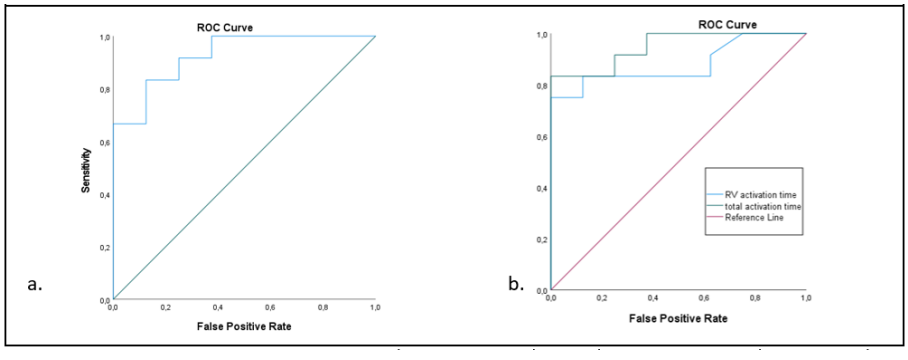

Figure 9. The ROC curves for Terminal Activation area, total activation time and RV activation

The figure shows the ROC curves for $aVAte_{20}$ *(blue on the left), tVAT (green on the right), and RVAT (blue on the right). The area under the curve (AUC) is 0.927 for the* $aVAte_{20}$*, 0.948 for the tVAT, and 0.880 for the RVAT.*

8.4.4 Morphology of the reconstructed epicardial signals

In the *controls,* the epicardial signals predominantly had a rS morphology at all RV segments except for the RVOT and the basal segment of the RVIW, where they had an rSr' morphology.

In the *ARVC patients,* the epicardial signals had a similar morphology as in the controls. However, all segments presented a higher variability in the morphology of the epicardial signals, where rSr' and qRs could also be seen, particularly at the RV base and at the apical segment of the RV inferior wall. Fractionated signals were present in 7/12 ARVC patients.

The *M-carriers* presented a similar morphology of the epicardial signals compared with the controls. In two cases, fractionated complexes were present.

The epicardial T-waves were most commonly positive at the whole RV in controls, except for the basal segment of the RVIW and RV basis, where they presented a more variable morphology. The ARVC patients most commonly had negative T-waves (10/12 cases), even if isoelectric and biphasic were also present. In the M-carriers, the T-waves were predominantly positive, except for the RV inferior wall and the RV base, where negative T-waves were most common. Isoelectric and biphasic T-waves were also present in 5/20 M-carriers.

8.5 ECG, Body Surface Mapping and ECGI findings in the ARVC cohort (a synopsis of Studies I, II, and IV)

8.5.1 Repolarization abnormalities

None of the controls in this study presented repolarization abnormalities on surface ECG or a pathologic repolarization pattern on the BSM recordings. Even if uncommon, negative and isoelectric epicardial T-waves were present in this group (Table 11).

In the ARVC group, 10/12 patients had a T-wave inversion on the right precordial leads V1-V3; in 11/12 patients, there appeared a T-wave inversion in the lateral leads (V5-V6 and/or aVL, I) and/or in the inferior leads (II, III, aVF). Two ARVC patients only had a T-wave inversion in the inferior leads, which is not a diagnostic criterion, either according to the 2010 TFC or according to the later implemented Padua Criteria.[19,229] However, all of the ARVC patients had a pathologic repolarization pattern in the BSM recordings and T-wave inversions on the epicardial signals (Table 11).

In the M-carriers group, only two individuals had negative T-waves on the precordial leads of the surface ECG. Both of them had a pathologic repolarization pattern according to the BSM recordings. A repolarization pattern 2 or 3 was observed in three more subjects with a totally normal surface ECG. All five subjects with a pathologic repolarization pattern had negative or isoelectric T-waves on the epicardial signals. Of the 15 remaining subjects with a normal repolarization pattern, four had negative or isoelectric epicardial T-waves on the RV anterior wall and RVOT, while six more subjects had this on the RV base and the inferior wall.

Table 11. Summary of the repolarization characteristics of the cohort.

		ECG			BSM	Epicardial signals/ ECGI				
	ID	TwI V1-V3	TwI V5-V6, I, aVL	TwI II, III, aVF	Repolarization pattern	Tw AW	Tw RVOT	Tw base	Tw IWa	Tw IWb
Controls	C1	-	-	-	1	+	+	-	+	+
	C2	-	-	-	1	+	-	Iso	+	+
	C3	-	-	-	1	+	+	Iso	+	+
	C4	-	-	-	1	-	+	-	-	-
	C5	-	-	-	1	+	+	+	+	+
	C6	-	-	-	1	+	+	+	+	+
	C7	-	-	-	1	+	+	-	Iso	-
	C8	-	-	-	1	Iso	-	Iso	-	-
ARVC patients	P1	-	-	+	3	+	+	Iso	-	-
	P2	+	-	-	2	-	-	-	-	-
	P3	+	+	-	3	-	-	-	-	-
	P4	+	+	-	2	-	-	Iso	-	-
	P5	+	-	+	2	-	-	-	-	-
	P6	+	+	+	3	-	-	-	-	-
	P7	+	-	+	3	-	Biph	-	-	-
	P8	+	+	-	3	Iso	-	Iso	Iso	Iso
	P9	+	+	+	3	-	-	-	-	-
	P10	+	+	-	3	Biph	Biph	Biph	-	-
	P11	+	-	+	3	Iso	-	-	-	-
	P12	-	-	+	3	Iso	-	Iso	-	-
Genotype-positive phenotype-negative subjects	G1	-	-	-	1	+	+	+	+	+
	G2	-	-	-	1	+	+	Iso	Iso	-
	G3	-	-	-	1	+	+	-	-	-
	G4	-	-	-	1	+	+	+	+	-
	G5	-	-	-	1	+	+	-	+	-
	G6	-	-	-	1	+	+	+	+	+
	G7	-	-	-	1	-	-	-	-	-
	G8	-	-	-	1	-	Iso	-	-	-
	G9	+	-	-	2	-	Iso	-	-	-
	G10	-	-	-	1	+	+	-	+	-
	G11	-	-	-	2	Iso	Iso	Iso	-	-
	G12	-	-	-	2	+	-	-	-	-
	G13	-	-	-	1	+	+	-	-	-
	G14	-	-	-	1	+	+	+	-	-
	G15	-	-	-	2	+	-	-	-	-
	G16	-	-	-	1	+	+	Iso	+	+
	G17	-	-	-	1	+	+	+	+	+
	G18	-	-	-	1	Iso	Iso	Iso	Iso	Iso
	G19	+	-	-	3	-	-	-	-	-
	G20	-	-	-	1	Iso	Iso	-	-	-

The table summarizes the main findings of Studies I, II, and IV regarding repolarization and compares them with the findings from a 12-lead ECG. (Tw: T-wave, TwI: T-wave inversion, AW: anterior wall, IWa: apical segment of inferior wall, IWb: basal segment of inferior wall, P: positive, N: negative, Iso: isoelectric, Biph: biphasic, Repolarization pattern: Refers to the repolarization pattern detected by BSM, where repolarization pattern 1 is the normal pattern and the repolarization patterns 2 and 3 are abnormal.)

8.5.2 Depolarization abnormalities

None of the controls fulfilled any of the depolarization criteria according to the 2010 TFC.[19] Late potentials were present in two controls. None of them presented a prolonged QRS dispersion or a pathologic epicardial activation assessed by ECGI.

In the ARVC group, 11/12 cases fulfilled the diagnostic depolarization criteria, but only 5/12 had a prolonged ECG-QRS dispersion. BSM-QRS dispersion was prolonged in all but one case. All of the ARVC patients presented pathologic $VAte_{20}$. The majority (11/12 subjects) presented at least 2/3 of the following parameters: $aVAte_{20}<68cm^2$, tVAT >76msec, and RVAT >49msec.

In the M-carriers group, only 5/20 subjects fulfilled the depolarization ECG criteria; two of them had a slightly prolonged ECG-QRS dispersion (42 msec). Four M-carriers presented a prolonged BSM-QRS dispersion; none of them fulfilled any of the ECG depolarization criteria. Out of the five subjects with late potentials at SAECG, three of them, all fulfilling 3/3 of the criteria for late potentials, had a pathologic pattern of $VAte_{20}$ in ECGI. Ten subjects in total presented abnormal $VAte_{20}$, involving additional parts of the RV; all, except for one, had a small $aVAte_{20}$ and/or prolonged tVAT/ RVAT.

8.5.3 Comparison of repolarization and depolarization characteristics of the cohort

The depolarization and repolarization abnormalities recorded in the M-carriers did not overlap. Although 2/5 M-carriers with a pathologic repolarization pattern on the BSM recordings also had abnormal $VAte_{20}$, the remaining three did not. Likewise, 8/10 M-carriers with an abnormal $VAte_{20}$ had no repolarization abnormalities on the ECG or the BSM recordings.

Table 12. Summary of the depolarization characteristics of the cohort.

		ECG-SAECG				BSM	Epicardial activation/ ECGI			
	ID	EW	TAD >55ms	LP criteria	ECG-QRS disp>40ms	BSM-QRS disp >40ms	Abnormal TA	$aVAte_{20}$ <68cm²	tVAT >76ms	RVAT (>49ms)
Controls	C1	-	-	1	-	-	-	-	-	+
	C2	-	-	0	-	-	-	-	-	-
	C3	-	-	0	-	-	-	-	-	-
	C4	-	-	0	-	-	-	-	-	-
	C5	-	-	0	-	-	-	+	-	-
	C6	-	-	0	-	-	-	-	-	-
	C7	-	-	0	-	-	-	-	-	-
	C8	-	-	1	-	-	-	-	-	-
ARVC patients	P1	-	-	3	-	+	+	+	+	+
	P2	-	+	3	+	+	+	+	+	+
	P3	-	+	3	+	+	+	+	+	+
	P4	+	+	3	-	+	+	-	-	-
	P5	-	+	3	-	+	+	+	-	+
	P6	+	+	3	+	+	+	-	+	+
	P7	-	-	3	-	+	+	+	+	+
	P8	+	+	3	-	+	+	+	+	+
	P9	+	-	3	+	+	+	+	+	+
	P10	+	+	3	-	+	+	+	+	-
	P11	-	-	0	-	-	+	+	+	+
	P12	+	+	3	+	+	+	+	+	+
Genotype-positive phenotype-negative subjects	G1	-	-	0	-	-	+	+	-	+
	G2	-	-	0	-	+	+	-	-	-
	G3	-	-	0	-	+	-	-	-	+
	G4	-	-	3	-	-	+	-	-	+
	G5	-	-	0	-	-	-	-	-	-
	G6	-	-	0	-	-	+	+	-	+
	G7	-	-	3	-	-	+	+	-	+
	G8	-	-	0	-	+	-	+	-	+
	G9	-	-	0	-	-	-	-	-	-
	G10	-	+	3	+	-	+	+	+	+
	G11	-	-	0	-	-	+	+	-	+
	G12	-	+	1	+	-	-	-	-	+
	G13	-	-	0	-	-	-	-	-	-
	G14	-	-	0	-	-	+	+	-	+
	G15	-	-	0	-	-	+	+	-	+
	G16	-	-	0	-	-	-	+	-	+
	G17	-	-	0	-	+	-	-	-	-
	G18	-	-	1	-	-	-	+	-	+
	G19	-	-	0	-	-	-	-	-	+
	G20	-	-	0	-	-	+	+	-	-

The table summarizes the main findings of studies I, II, and IV regarding depolarization and compares them with the findings from a 12-lead ECG. (EW: epsilon-wave, TAD: terminal activation duration, LP: late potential, disp: dispersion, TA: terminal activation, $aVAte_{20}$*: terminal activation area, tVAT: total activation time, RVAT: activation time of the right ventricle, ms: milliseconds)*

LP criteria: Refers to the number of LP criteria that are fulfilled.

8.6 Clinical characteristics, Family History, and Cardiac Symptoms Prior to Sudden Cardiac Death in ARVC (Study III)

8.6.1 Sociodemographic characteristics

The sex and age distribution of the 22 cases included in the study are presented in Figure 10. The educational level and family type did not differ statistically between the cases and the controls.

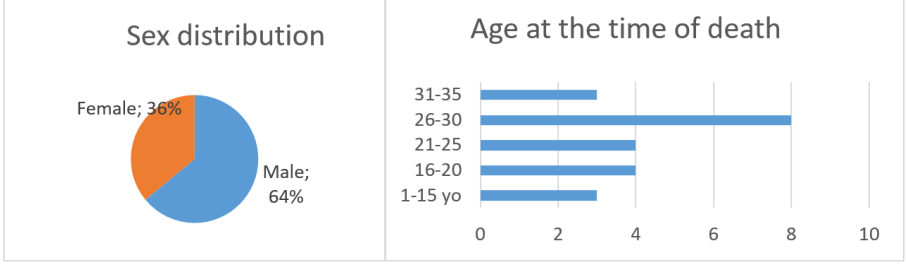

Figure 10. Sex and age distribution of all the cases

8.6.2 Medical history

Hospital visits:

According to national data from the NPR, 41% of the cases (9/22) had at least one hospitalization or outpatient hospital visit during the last six months prior to death, compared to only 17% (19/110) of the controls (OR 4.63 [95% CI: 1.35–15.8] P 0.010). A cardiac-related ICD-10 code was registered in 56% of the hospital visits in the cases, but in none of the controls.

Cardiac symptoms preceding SCD:

Fifteen cases (68%) had experienced symptoms during the last six months preceding SCD. The most common symptoms were palpitations (41%), syncope (27%), presyncope (27%), chest discomfort (27%), and seizures (14%). Eight subjects (36%) sought medical care during this period (Figure 11). Three cases were diagnosed with myocarditis, right ventricular outflow tract (RVOT)-tachycardia, and ARVC, respectively. Two cases received a dyspepsia diagnosis, while no diagnosis was received in three cases.

Cardiac disease preceding SCD:

Only one subject had an ARVC diagnosis prior to SCD; this patient had a history of non-sustained VT and was diagnosed three years prior to death. A

history of ventricular arrhythmias was observed in three more cases. In one case, the patient was diagnosed with benign RVOT tachycardia. Another case had survived a cardiac arrest at the age of 10 and was diagnosed with long QT-syndrome (LQTS). The last case had documented VES during a neck surgery, but further investigation was not performed. None of these subjects had received an ICD.

Cardiac examination preceding SCD:

Echocardiography was performed in only four cases, two of them consulting ECG because of syncope or presyncope, one because of seizures and the last one within the framework of family screening. The echocardiographic criteria for ARVC were fulfilled in only one case, and the patient was already diagnosed with ARVC. Two cases presented non-sustained ventricular tachycardias and >500 extrasystoles/ 24 hours on Holter monitoring, fulfilling a minor criterion according to the 2010 TFC.[19]

ECG recordings were performed in 11 cases, where three of them were within the last six months before the SCD. Epsilon wave was suspected in only one case, who also had a T-wave inversion in V1 and V2, but no further investigation was performed. Precordial T-wave inversion was observed in three more cases; in one case, an evaluation with echocardiography and 24 hours Holter monitoring confirmed the ARVC diagnosis, while in the other two cases, no further investigation was performed. Four cases, in total, would fulfil the minor or major electrocardiographic criteria according to the 2010 TFC.[19]

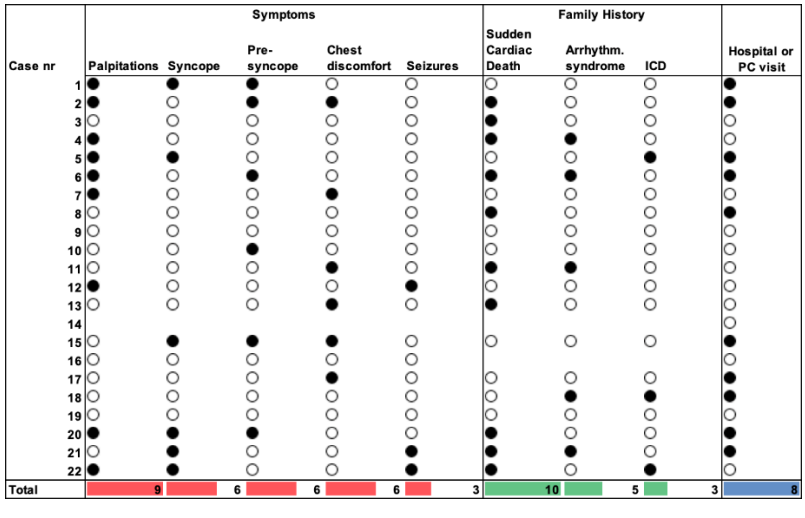

Figure 11. Symptoms, family history, and medical visits six months prior to SCD due to ARVC.

The figure summarizes the symptoms reported during the last six months prior to death, the family history, and the hospital or PC visits for each case. Ten cases in total had a medical contact, of which 8 due to cardiac related symptoms.

8.6.3 Family History

In ten cases (45%), there was a family history of SCD, among first-degree relatives in two cases and among second-degree relatives in eight cases. In seven cases (32%), there was a SCD history among individuals younger than 40 years old. In four cases (18%), two or more relatives had died suddenly.

Moreover, in two cases (9%), there was a living relative with an arrhythmogenic syndrome, one with ARVC and one with Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) and in three cases (14%), there was a living relative with an ICD (Figure 11).

8.6.4 History of physical activity

Five cases (23%) participated in competitive sports, twelve (55%) participated in recreational sports, whereas two (9%) did not participate in any sports activities. In three cases (14%), the history of physical activity was unknown. The majority (68%) participated in high dynamic physical activity, such as soccer, ice hockey, basketball, running, floorball, or swimming.

8.6.5 Circumstances of death and autopsy findings

In most cases (59%), SCD occurred during rest, sleep, or daily routine activities. Nine subjects (41%) died while exercising, two of them during competitive sports. Seven subjects (32%) experienced prodromal symptoms immediately before the SCD, including chest pain, palpitations, seizures, and nausea. Five subjects (23%) had no symptoms at all, while in ten cases (45%), the death was unwitnessed.

All cases received a post-mortem ARVC diagnosis, after a forensic autopsy (55%) or a clinical autopsy (45%). In thirteen cases (60%), no myocardial changes were detected macroscopically, but only after a histopathological examination. The myocardial changes were biventricular in twelve cases (55%).

9. Discussion

9.1 The potential role of Electrocardiographic Imaging in ARVC diagnosis (Studies I, II, and IV)

This doctoral project is the first study that investigates the potential role of ECGI in early ARVC diagnosis. Previous studies using ECGI have revealed electrophysiological abnormalities in ARVC patients in various stages of the disease.[278,279] These studies, however, have focused on the analysis of the activation maps of the epicardial signals and on populations with an established disease.

In the present study, we explored the diagnostic capability of ECGI in patients with a definite ARVC diagnosis, but we also focused on a much healthier population, i.e., M-carriers without a clear ARVC phenotype. This group of genetically predisposed individuals who could be in an early stage of the disease has not previously been investigated with ECGI. This is an important group that requires extensive investigations and follow-ups and which should benefit the most from an early diagnosis, thus preventing or managing in time potential life-threatening arrhythmias. Accordingly, we included M-carriers without a history of ventricular arrhythmias or structural abnormalities. Isolated depolarization or repolarization criteria, however, were permitted in this group, in order to investigate consistencies with ECGI even in these early stages of the disease.

Additionally, in this project, we investigated the usefulness of the whole spectrum of data obtained by ECGI, i.e., both the body surface signals recorded by the vest and the reconstructed epicardial signals, which is a novel approach. Our data suggest that both body surface signals and reconstructed epicardial signals could provide us with important information on the electrophysiological properties of the myocardium, improving the diagnostic yield of ARVC.

9.1.1 Repolarization abnormalities revealed using Body Surface Mapping (Study I)

The BSM recordings unmasked abnormal repolarization patterns in all the ARVC patients (two of whom had no T-wave inversions on ECG) and in 25% of the M-carriers (three of whom had no T-wave inversions on surface ECG).

These results suggest that the BSM system is more sensitive when it comes to revealing the repolarization abnormalities compared to the ECG; moreover, the results support its diagnostic capability in the early stages of ARVC.

The high number of electrodes on the BSM vest permits the recording of surface ECG signals with a much higher resolution compared to conventional ECG. The electrodes in the frontR panel, as well as those in the middle and lower part of the frontL panel, are anatomically closer to the RV and can thus record the RV electric activity more precisely. The conventional 12-lead ECG has a limited capacity to record signals from the RV, which is represented only by the right precordial leads V1-V3. The additional recording with the V4R lead also revealed the T-wave inversions in the majority of the ARVC patients (83%), but was unspecific, as half of the controls and M-carriers had the same finding (Table 5).

The characteristic negative concordant T-waves in both the right panels and the gradual transition of the T-waves in the frontL panel from the negative concordant pattern in the upper part, to the positive disconcordant in the middle and finally, positive concordant at the bottom, probably reflect the gradual change of the T-wave and QRS morphology in the precordial ECG leads. The absence of this gradual transition of the T-waves in the ARVC patients and some M-carriers, demonstrating more negative T-waves in the whole frontL panel, reflects the anterior precordial T-wave inversions noted on conventional ECG. The completely deranged repolarization pattern 3 noticed in some of the ARVC patients and one M-carrier also reveals positive T-waves in the back panels and a high number of isoelectric/ biphasic T-waves, which is not encountered in the other two patterns. Even if this finding is not investigated and described in other previous studies, it implies the presence of more extensive repolarization abnormalities which reflect on the whole thorax.

Multi-electrode BSM systems have previously been used to study the ventricular repolarization in ARVC patients.[194,315] QRST integral maps, created using a 62-lead BSM system, have revealed negative QRST integrals on the right frontal part of the thorax in ARVC patients, a pattern that was different compared to controls or patients with idiopathic RVOT tachycardia.[315] Similarly, in another study based on T-wave integral maps, created by a 120-lead BSM system, lower T-wave integrals were revealed in the right lower front part of the torso in ARVC patients, compared to controls and patients with idiopathic RVOT tachycardia.[194] These findings are consistent with our results, where the abnormalities of the repolarization patterns in the ARVC patients were first observed in the lower part of the frontL panel and in the right panels. However, in these studies, no genotype-positive phenotype-negative subjects were included. Thus, our results reveal for the first time such abnormalities even in the early stages of the disease.

9.1.2 Depolarization changes / QRS dispersion evaluated using Body Surface Mapping (Study II)

In study II, a high BSM-QRS dispersion (>40msec) could differentiate almost all the ARVC patients (11/12) from the controls. Moreover, some M-carriers (4/20) had slightly elevated BSM-QRS dispersion, possibly indicating early depolarization abnormalities. The higher BSM-QRS dispersion in the ARVC patients and some M-carriers was probably caused by the QRS prolongation in the affected areas, indicating a local conduction delay. This was supported by the observation that the ARVC patients had significantly higher maximum QRS durations, although the minimum values were similar in all study groups.

ECG-QRS dispersion was higher in the ARVC patients compared to the other groups. However, it was inferior to BSM-QRS dispersion in discriminating the ARVC patients from the controls. The higher sensitivity of the BSM-QRS dispersion compared to the ECG-QRS dispersion is probably explained by the larger number of electrodes, which enables the detection of QRS prolongation in leads of the vest, which are not represented by a conventional ECG. Indeed, the longest QRS durations in the ARVC patients were located in the frontR panel in four cases, backL panel in one case and upper part of the frontL panel in one case; none of these leads are covered by surface ECG (Table 9).

Even though all the ARVC patients with a high ECG-QRS dispersion had a high BSM-QRS dispersion as well, only a few patients with high BSM-QRS dispersion also had a high ECG-QRS dispersion. These results may indicate that a prolonged ECG-QRS dispersion could reflect more extensive depolarization abnormalities. This could probably explain why in previous studies a higher ECG-QRS dispersion has been considered a marker for ventricular arrhythmias and SCD.[313,316] A high QRS dispersion detected even by an ECG could indicate a more advanced stage of the disease and thus, hypothetically a worse prognosis.

However, the M-carriers with an abnormal ECG-QRS dispersion and those with an abnormal BSM-QRS dispersion did not overlap, suggesting that caution is required in the interpretation of the results in patients with QRS dispersion values just above the limits and without other signs of the disease, as the clinical implication of such findings remains unclear.

9.1.3 Epicardial ventricular activation evaluated using Electrocardiographic Imaging (Study IV)

In study IV, ECGI revealed a terminal ventricular activation ($VAte_{20}$) that involved only segments of the RV in the ARVC patients, a pattern that differed from the controls, in whom $VAte_{20}$ always involved RVOT and the LV base. The fact that no LV segments were involved in $VAte_{20}$ in the ARVC group suggests that the electrical conduction was locally delayed in the RV and was continued even after the LV activation was completed. The most important finding in this study, however, was the fact that even 50% of the M-carriers presented an abnormal terminal ventricular activation pattern, involving parts of the RV, other than the RVOT. In this sub-group, the LV base was still activated during the $VAte_{20,}$ but some segments of the RV were also activated late, occupying a part of the $VAte_{20}$.

The smaller $aVAte_{20}$ noted in the ARVC patients and in the subgroup of M-carriers with an abnormal terminal ventricular activation pattern compared to the controls reflects the slow spreading of the activation front within these affected areas. It is also noteworthy that although the ARVC patients had both prolonged tVAT and RVAT, compared to the controls, consistent with previous reports,[278,279] the M-carriers with an abnormal $VAte_{20}$ only had a prolonged RVAT, but a normal tVAT. This finding may suggest a lower degree of histological/cellular abnormalities in the M-carriers compared to the ARVC patients. While ARVC patients present extensive lesions which cause delayed RV activation, and further the LV activation, M-carriers' lesions are limited, affecting only the RV segments and causing a delayed local activation which does not exceed the LV activation.

Several other observations in this study are interesting, even if not always statistically significant. Different earliest and/or latest activation sites were observed in the majority of the ARVC patients (7/12) and M-carriers (12/20) compared to the controls and were in agreement with previous reports.[278,279] An abnormal site of latest RV activation indicates a locally delayed conduction, causing an activation later than RVOT, which usually activates last. Similarly, an abnormal site of earliest RV activation probably indicates a delayed activation in the RV anteroparaseptal regions, which usually activates first. The fractionated electrograms which were found in the majority of the ARVC patients and in two M-carriers are a common finding in ARVC and also suggest a delayed local depolarization.[317-319]

The morphology of the epicardial T-waves has not previously been studied. However, the higher prevalence of negative, isoelectric, and biphasic epicardial T-waves among the ARVC patients and the M-carriers compared to the controls may reflect repolarization abnormalities.

All these findings may suggest that electrophysiological disturbances are present in ARVC patients and in M-carriers in the concealed phase of the disease and can be detected using ECGI.

9.1.4 The clinical significance of the BSM and ECGI findings

In previous studies, the ECG repolarization abnormalities have been associated with RV dilatation and dysfunction in ARVC patients.[198,203,204] It has also been suggested that the extent of T-wave inversion in ECG correlates with the electroanatomic voltage abnormalities and the extent of the electroanatomic RV scar recorded in ARVC patients.[205,206] Thus, the repolarization changes recorded by the BSM system in the ARVC patients in *study I* may also reflect electrophysiological abnormalities of the diseased tissue, probably caused by the fibrofatty replacement of the myocardium. Likewise, the abnormalities of the repolarization detected in the M-carriers could probably indicate early changes in the electrophysiological properties of the diseased tissue, which were not detectable by the conventional investigations, but still affected the RV repolarization.

The extent of conduction delay and scarring revealed by endocardial mapping in ARVC patients has been suggested as being related to the extent of ECG depolarization abnormalities.[213] It has also been suggested that a prolonged QRS dispersion may reflect a right ventricular dilatation, larger RVOT area, and larger RV end-systolic and end-diastolic volumes.[314] Thus, the local QRS prolongation detected in the ARVC patients by the BSM system in *study II* could reflect areas with structurally affected myocardium and conduction delay.

The delayed conduction within the diseased tissue is a well-described feature in ARVC.[320,321] The electrical stability of the myocardium depends on the integrity of the electrical coupling of the myocytes, which, in turn, depends on the integrity of the cell-to cell adhesion in the intercalated discs.[322] In ARVC, the defected desmosomal genes encode the dysfunctional desmosomal proteins, leading to the interruption of the mechanical and electrical coupling of the myocytes.[90-92,323,324] Consequently, the conduction of the electrical signals is disturbed, causing conduction delay and electric instability.[325] The conduction delay revealed with ECGI in the ARVC patients in *study IV*, expressed as an abnormal terminal ventricular activation, prolonged tVAT and RVAT, and fractionated electrograms, may, therefore, mirror the electric uncoupling of the myocytes.

Previous studies imply that even patients with early stages of ARVC without any detectable structural abnormalities can develop conduction delays. Experimental and human studies in ARVC subjects suggest that electrical abnormalities, in the form of delayed conduction, precede the structural ones.[326,327] Clinical studies also suggest that ventricular pacing can reveal a delayed conduction and repolarization dispersion, even in patients with early stages of the disease.[326,327] Finally, clinical follow-up of relatives with a risk of ARVC has revealed that the electrical progress of the disease precedes the development

of structural abnormalities.[22] All these data suggest that early electrophysiological abnormalities may be present even before structural or ECG abnormalities are apparent. The abnormal QRS dispersions detected in the M-carriers in *study II*, could therefore indicate early and less extensive cellular changes that can cause local conduction delay and QRS prolongation without causing structural or pronounced electrocardiographic abnormalities. Similarly, the abnormal epicardial activation pattern, as well as the delayed activation of the RV alone, presented in the M-carriers in *study IV*, could declare a mild stage of ARVC.

9.1.5 ECG, Body Surface Mapping, and ECGI findings in an ARVC cohort (a synopsis of Studies I, II, and IV)

The comparison of the ECG findings with the findings from the BSM system and ECGI, summarized in Tables 11 and 12, reveals some important observations.

All the ARVC patients in this study presented abnormal repolarization patterns in the BSM recordings and T-wave inversions on epicardial signals, even in the two cases without T-wave inversions on ECG. Three M-carriers without repolarization ECG criteria presented abnormal repolarization patterns, and ten more had epicardial T-wave inversion in segments of the RV. The analysis of body surface signals and reconstructed epicardial signals, thus, was more sensitive when it comes to detecting the repolarization disturbances compared to surface ECG. However, epicardial T-wave inversion was also present in some controls, indicating that this finding was rather unspecific.

All but one of the ARVC patients fulfilled at least 2/3 of the criteria for epicardial activation that we introduced in study IV ($aVAte_{20}$<68cm^2, tVAT >76msec, and RVAT >49msec), which could be useful diagnostic markers. The last patient had a normal $aVAte_{20}$ and normal tVAT and RVAT, but the activation map illustrated a $VAte_{20}$ involving the RV base and RV apex, which was abnormal. A possible explanation could be the fact that this patient was diagnosed with ARVC just a few months before the study was conducted and was still in the early stages of the disease. Therefore, the evaluation of the pattern of the $VAte_{20}$, beyond the area and the timing, is very important in order to detect abnormalities (Table 12). The high percentage of M-carriers with delayed conduction in segments of the RV, other than the RVOT, indicates that ECGI is a sensitive method and can detect slow conduction even in early stages of the disease, consistent with a concealed phase, before the development of abnormalities on surface ECG or body surface signals.

It is well known that the fibrofatty replacement of the affected myocardium in ARVC is initiated in the epicardium or mid myocardium before spreading to the endocardium, causing transmural lesions.[98] Clinical studies evaluating the substrate for ventricular arrhythmias using endocardial mapping support

that the epicardial lesions are more extensive than the endocardial in ARVC patients.[328] Our findings in this study further suggest that epicardial repolarization and depolarization disturbances occur early and could be an early sign of disease progression.

The fact that the repolarization and depolarization abnormalities uncovered in this study do not always co-exist in the M-carriers implies the existence of different pathophysiological pathways in the early stages of the disease, leading to either a disturbed repolarization or a delayed depolarization. With the progression of the disease, probably both repolarization and depolarization get affected, explaining why all the ARVC patients in this study presented both an abnormal repolarization pattern and abnormal terminal ventricular activation pattern. Thus, as the current diagnostic criteria suggest, repolarization and depolarization abnormalities do not always co-exist, and the assessment of both is crucial for a correct diagnosis.[19]

9.1.6 Limitations of the BSM-detect ARVC study and technical considerations

The ***BSM-detect ARVC study*** was an explorative study, and the cohort was rather small. Moreover, the ARVC patients included had a typical ARVC phenotype, with predominantly RV involvement, and the majority of them had a mutation in the desmosomal genes. The present results should, therefore, be confirmed in larger and more heterogeneous cohorts with a broader spectrum of ARVC phenotypes.

MRI was not included in the study protocol and was not routinely performed in all study subjects. We therefore cannot exclude that some of the M-carriers had minimal myocardial abnormalities, consistent with ARVC and only detectable by MRI.

The ECGI is a new technology which requires specific equipment and trained staff. The vest used for the recording of the body surface signals is still overpriced, restricting its usage to a small number of patients. Moreover, the commercially available CardioInsight software is used for the processing and analysis of the epicardial signals only. The development of a software that also permits the analysis of the body surface signals is mandatory in order to evaluate our results in larger studies.

9.2 Clinical characteristics, Family History, and Cardiac Symptoms Prior to Sudden Cardiac Death in ARVC (Study III)

Study III is the first nationwide study investigating the clinical characteristics of SCD victims due to ARVC in Sweden. Even if the cohort is small, the results have important clinical implications.

9.2.1 Symptoms and medical contacts prior to SCD

The main finding in this study was the high prevalence of cardiac related symptoms and medical contacts during the last six months prior to death. The most common symptoms reported were palpitations, syncope/pre-syncope, and chest discomfort, consistent with previous reports.[13,124,329,330] The healthcare visits were also significantly more frequent among the cases compared to the matched controls. Despite this, symptoms were often underestimated, and only a few subjects were referred further for additional follow-up and clinically evaluated with electrocardiography or echocardiography. Even in these cases, discrete ECG abnormalities were often overseen and misinterpreted as normal.

These results confirm previous studies which report the same trend of underestimating the cardiac symptoms among the young.[13,329] They further indicate how critical it is to correctly and carefully evaluate young people seeking care for cardiac symptoms; a timely evaluation could be lifesaving.

9.2.2 Family history

A comprehensive evaluation of a three-generation family history revealed a high prevalence of relatives with SCD (45% of all cases). There was more than one affected relative in 18% of all cases. However, the family history was rarely commented on in the medical records and was often incomplete. An interesting and important observation is also the fact that the affected individuals were more often second-degree relatives (36% of all cases). These results indicate the incomplete penetrance of the disease, a well-recognized feature of ARVC, and the importance of a comprehensive three-generation family history for individuals at risk.[21,235,331]

9.2.3 Clinical significance of findings in Study III

Study III reflects the real life praxis on the management of young people with cardiac related symptoms and emphasizes some important improvements that need to be made.

An awareness by physicians on the alarming symptoms among young people as well as education on appropriate management are imperative to achieve an early detection of ARVC and prevent SCD. Young people with such symptoms should be carefully evaluated, including a personal and family history. ECG should be carefully reviewed by physicians with competence within the field of cardiology. Further investigation should be performed whenever needed.

Study III also emphasizes another important point: the importance of the family screening in cases of SCD in young age. The systematic clinical evaluation and education of family members on the alarming symptoms that should raise a suspicion of cardiac disease are very important. By raising awareness among relatives at risk, we could ensure that they seek medical care in time.

9.2.4 Limitations of Study III

Study III was a retrospective study based on the manual revision of the autopsy reports and death certificates of the SCD victims. As all autopsies were performed locally in several Forensic or Hospital Clinical Pathology departments, several different local protocols were available at the time of the investigation (2000–2010). In order to overcome this limitation, all the autopsy reports were manually revised in accordance with the 2010 TFC and the European guidelines for autopsy investigation in SCD.[19,332] However, it cannot be excluded that some ARVC cases remained undiagnosed in the SUDDY cohort and were classified as other diagnoses.

Moreover, this is a study of ARVC cases with the worst outcome, as only deceased SCD victims were included. Subjects who survived a cardiac arrest or those ARVC patients who did not die suddenly were not included in the SUDDY cohort.

Finally, the data collection through phone calls and questionnaires to family members may lead to under-reporting or over-reporting of the symptoms and signs.

10. Conclusions

Based on the results of this thesis, we can conclude that, although a lot of progress has been made in the field of ARVC during the last few years, the disease is underdiagnosed, and SCD can still be the first manifestation. A lot of effort is required to increase an awareness of the disease and its potential risks for young individuals with cardiac related symptoms, who should undergo comprehensive clinical investigation, including a detailed medical and family history.

Genotype-positive relatives of ARVC patients can present early signs of the disease although they are asymptomatic, and no ECG abnormalities or structural changes can be seen in clinical investigations. The comprehensive analysis of the body surface signals recorded by the ECGI vest can enhance the diagnosis by revealing abnormal repolarization patterns or prolonged QRS dispersion. The diagnostic yield of BSM signals is better compared to a 12-lead ECG.

The analysis of the reconstructed epicardial signals can further improve the diagnostic yield of ARVC, by confirming the presence of areas with delayed activation in ARVC patients and by revealing similar areas in genetically predisposed relatives. The findings in the M-carriers imply the existence of discrete histopathologic abnormalities, undetectable by ECG or echocardiography, which may represent the concealed phase of ARVC. The restricted epicardial area activated during the terminal part of the epicardial ventricular activation and the prolonged time required for the depolarization of the RV epicardium suggests the delayed conduction in these areas due to early changes in the cellular level of the affected myocardium. Therefore, the $aVATe_{20}$ and RVAT could be useful markers for early diagnosis.

All the ARVC patients present with abnormal repolarization patterns and depolarization abnormalities on epicardial signals and body surface signals, but in M-carriers, depolarization and repolarization abnormalities do not always co-exist. This observation suggests that in the early stages of the disease, different pathophysiological pathways may be activated, leading to the disturbance of either the normal repolarization or depolarization, while in advanced disease, both repolarization and depolarization are affected.

11. The importance of the findings and future perspectives

A major clinical challenge in the ARVC field, nowadays, is the management of the genotype-positive phenotype-negative family members detected through family screening, as well as the management of the healthy individuals in ARVC families without a known genotype. Given that ventricular arrhythmias and SCD can occur during the early stages of the disease, an early diagnosis is of high clinical significance.[124]

The ***BSM-detect ARVC study***, although explorative, gives new insights into the evolution of the electrophysiological abnormalities in ARVC. The detection of minor repolarization and depolarization disturbances in M-carriers, which could reflect a concealed phase of the disease, can have an important impact on diagnosis. ECGI, with the multiple lead vest and the reconstructed epicardial signals, could facilitate the serial evaluation of individuals at risk in a non-invasive manner and could enhance an early diagnosis. The validation in larger studies, including cardiac MRI, which was not included in this study, could open the road for its broader usage. Further evaluation in prospective studies could be valuable in order to investigate whether these findings reflect a higher arrhythmic risk and could also have prognostic value. Moreover, technological improvements are required to make ECGI more easily accessible and cost-effective.

Even if ARVC is a relatively uncommon cardiomyopathy and even if cardiac related symptoms in young people are more often benign, the consequences of the underestimation of these symptoms and the inadequate investigation can be dramatic, leading in the worst case to SCD. The results of ***study III*** enlighten the importance of careful evaluation of young individuals who seek medical care with cardiac symptoms and emphasize the important role of conducting a comprehensive family and medical history, in an attempt to raise awareness both among patients and physicians. Genetic analyses on the study subjects are ongoing, in an attempt to confirm the diagnosis and investigate a potential mismatch between their genetic and phenotypic profile.

12. Sammanfattning på svenska (Summary in Swedish)

ARVC är en ärftlig kardiomyopati som drabbar desmosomer. När desmosomerna drabbas, den mekaniska och elektriska förbindelse mellan myocyterna försvagas och det normala myocardium ersätts av fibrotisk och fett vävnad. Höger kammare brukar drabbas först, men sjukdomen kan involvera båda kammare. Det vanligaste klinisk manifestation är ventrikulära arytmier, från enstaka extraslag till ventrikeltakykardi och plötsligt död och de kan utvecklas även i tidig fas av sjukdomen. Den tidiga diagnosen är därför avgörande för att förhindra plötsligt död.

I BSM-detect ARVC studie, undersökte vi användbarheten av Electrocardiographic Imaging (ECGI), i ARVC diagostik. ECGI är en mapping system som registrerar elektriska signaler från bålen, med en 252-elektroder väst. Med hjälp av de signalerna, en matematisk algoritm och anatomisk information samlad av CT scan, återskapas de epikardiella signalerna och en tridimesionell bild av hjärtat skapas som demonstrerar den elektriska aktiviteten i epikardium.

I studie I och II, fokuserade vi på de yt-signalerna som registrerades av västen. Eftersom epikardiela signalerna återskapas av signalerna som registreras av de 252 väst-elektroderna, detta första steg var viktigt för att förstå om avvikelser i elektrisk aktivitet kunde detekteras av väst elektroderna för att senare speglas i de rekonstruerade epikardiella signalerna. Våra resultat i studie I och II var lovande och visade att avvikelser i båda repolarisation (förändrat repolarisations mönster, studie I) och depolarisation (förlängd ”BSM-QRS dispersion”, studie II) av myokardiet kan detekteras i ARVC patienter jämfört med friska kontroller, även när sådana förändringar inte fanns på vanligt yt-EKG. Dock, det viktigaste fynd i de två första studierna var att även en del av anlagsbärare kunde uppvisa förändrat repolarisations mönster (25% av anlagsbärare) och/ eller förlängd BSM-QRS dispersion (20% av anlagsbärare), trots att i de flesta fall inga repolarisations respektivt depolarisations EKG kriteria var uppfyllda. De ovanstående resultat indikerar att ECGI, med de 252 väst- elektroderna, kan prestera bättre som diagnostisk verktyg jämfört med yt-EKG och kan identifiera diskreta förändringar i en del av anlagsbärare, vilka skulle kunna beteckna en tidig fas av sjukdomen.

I studie IV, analyserade vi de rekonstruerade epikardiella signaler. Våra resultat visade att vänster kammare aktiverades tidigt i ARVC patienter and

under de sista 20msec av epikardiella aktiveringen depolariserades bara delar av höger kammare, till skilnad från kontroller, som uppvisade sista aktiveringen i RVOT och basala delen av vänster kammare. Ytan av områderna som aktiverades sist ($aVAte_{20}$) var mindre i ARVC grupp, medan durationen av den totala kammaraktiveringen (tVAT) och den aktiveringen av höger kammare (RVAT) var längre jämfört med kontrolgrupp. De fynden tyder på att vissa område av höger kammare har en mycket fördröjt aktivering pga förändringar på cell nivå som förhindrar konduktionen av de elektriska signalerna. I anlagsbärargrupp observerades en normal epikardiel aktivering (som involverade RVOT och basala delen av vänsterkammare) i 50% av fallen, medan i resten 50% noterades flera område av höger kammare med sen aktivering. Den sub-group med sen aktivering i andra delar av höger kammare än i RVOT hade mindre $aVAte_{20}$ och längre RVAT jämfört med resten, medan tVAT var det samma. De här fynden kan indikera en lokal fördöjd aktivering i högerkammare som dock inte är såpass uttalad för att påverka aktiveringstiden av både kammare. Faktumet att område med sen aktivering detekterades i hälfen av anlagsbärare är en väldigt viktig observation, vilket tyder på en pågående process som startar tidigt.

Det måste ändå betonas att BSM-detect ARVC studie var baserad på en liten kohort, och de ovanstående resultat av studie I, II and IV, kräver validering i större kohorter. Implementering av en sådan icke invasive teknik som kan detektera diskreta elektrofysiologiska förändringar i genetiskt predisponerade individer, skulle dock facilitera tidig diagnostik och behandling med enda ändamål att förhindra plötsling död.

I studie III, som är en substudie av SUDDY databas, identifierade vi och kartlagde fenotypiskt alla unga (1-35 års ålder) individer som dött plötsligt i en obduktionsverifierad ARVC mellan 2000 och 2010. Totalt, identifierades 22 individer. Data samlades från flera nationella register, intervjuer med anhöriga och journalgenomgång. En stor andel av kohorten (68%) hade hjärtrelaterade symptom de sista 6 månader innan döden (de vanligaste symptomen var hjärtklappning, syncope och presyncope) och 36% hade sökt vård för detta. Data från NPR visade också flera registrerade kontakter med sjukvården under de sista 6 månaderna jämfört med matchade kontroller. Trotts detta, någon adekvat klinisk värdering var sällan genomförd. Bara en individ hade en ARVC diagnos innan dödsfallet. En viktig observation i studien var också att 45% av fallen had en familjanamnes av plötsligt död, men bara 9% hade familjanamnes i första grads anhöriga. Dem ovanstående resultaten betonar en olycklig trend att underskatta hjärtrelaterade symptom hos unga individer. En omfattande klinisk bedömning av unga symptomatiska patienter, inklusivt en detaljerad 3-generations familjanamnes är avgörande för att kunna identifiera individerna i riskzonen och förhindra plötslig död.

13. Aknowledgements

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