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"Advances in Electrocardiographic Features in Arrhythmogenic Right Ventricular Cardiomyopathy"

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SUMMARY

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic heart muscle disease characterized by electrical instability leading to ventricular arrhythmias and sudden cardiac death. The hallmark pathological lesion of ARVC is the transmural loss of the myocardium of the right ventricular (RV) free wall with replacement by fibro-fatty tissue. Three-dimensional electroanatomic voltage mapping (EVM) by CARTO system (Biosense-Webster, Diamond Bar, California) allows identification and characterization of low-voltage regions, i.e. “electroanatomical scars” (EAS), which in patients with ARVC correspond to areas of fibro-fatty replacement. Although the technique has been demonstrated to enhance the accuracy for diagnosing ARVC, its value for arrhythmic risk stratification remains to be established. Furthermore, the clinical utility of EVM for scar quantification and risk assessment is limited by its invasive nature, low availability and high costs. Thus, in daily clinical practice there is the need of a non-invasive test such as 12-lead electrocardiogram (ECG) for prediction of the amount of RV myocardial scar lesion and assessment of arrhythmic risk. Previous studies demonstrated an association between ECG repolarization/depolarization abnormalities and RV mechanical dilation/dysfunction. In fact, T wave inversion in right pericardial leads is the most common ECG abnormality of ARVC. However, the presence of T wave inversion in leads V1-V3, known as persistence of the juvenile pattern of repolarization, may also be observed in about 3% of healthy adults. The current perspective is that, at variance with healthy subjects, right precordial NTWs persist with exercise in ARVC patients. However, this view is not supported by systematic scientific data.

Objective

In this work, we aimed to further study some of the electrocardiographic features of ARVC. First, we assessed the prognostic value of EAS detected by EVM and its correlation with various non-invasive characteristics of ARVC, including abnormalities detected by surface ECG. Second, we studied the exercise-induced changes in right precordial negative T waves in patients with ARVC and in a group of healthy young individuals with persistence of the juvenile repolarization pattern

Methods and results

We first studied 69 consecutive ARVC patients (47 males; median age 35 years [28–45]) who underwent electrophysiological study and both bipolar and unipolar EVM. The extent of confluent bipolar (<1.5 mV) and unipolar (<6.0 mV) low-voltage electrograms was estimated using the CARTO-incorporated area calculation software. Fifty-three patients (77%) showed ≥1 RV electroanatomic scars with an estimated burden of bipolar versus unipolar low voltage areas of 24.8% (7.2–31.5) and 64.8% (39.8–95.3), respectively (P=0.009). In the remaining patients with normal bipolar EVM (n=16; 23%), the use of unipolar EVM unmasked ≥1 region of low-voltage electrogram affecting 26.2% (11.6–38.2) of RV wall. During a median follow-up of 41 (28–56) months, 19 (27.5%) patients experienced arrhythmic events. At multivariate analysis, the only independent predictor was the bipolar low-voltage electrogram burden (hazard ratio=1.6 per 5%; 95% confidence interval, 1.2–1.9; P<0.001). Patients with normal bipolar EVM had an uneventful clinical course.

Then we further analyzed a subgroup including 49 patients [38 males, median age 35 years] with ARVC and an abnormal EVM by CARTO system. At univariate analysis, the presence of epsilon waves, the degree of RV dilation, the severity of RV dysfunction and the extent of negative T-waves correlated with RV-EAS% area. At multivariate analysis, the extent of negative T-waves remained the only independent

predictor of RV-EAS% area (B=4.4, 95%CI 1.3-7.4, p=0.006) and correlated with the arrhythmic event-rate during follow-up (p=0.03).

In a different cohort, we assessed the prevalence and relation to the clinical phenotype of exercise-induced right precordial negative T wave changes in 35 ARVC patients (19 males, mean age 22.2±6.2 years). Forty-one healthy individuals with right-precordial negative T waves served as controls. At peak of exercise, negative T waves persisted in 3 ARVC (9%) patients, completely normalized in 12 (34%) and partially reverted in 20 (57%). ARVC patients with or without negative T waves normalization showed a similar clinical phenotype. The overall prevalence of right precordial T-waves changes during exercise (normalization plus partial reversal) did not differ between ARVC patients and controls (92% versus 88%, p=1.0), while there was a statistically non significant trend towards a higher prevalence of complete normalization in controls (59% versus 34%, p=0.06).

Conclusion

In conclusion, our results showed that the extent of bipolar RV endocardial low-voltage area was a powerful predictor of arrhythmic outcome in ARVC independently of arrhythmic history and RV dilatation/dysfunction. A normal bipolar EVM characterized a low-risk subgroup of ARVC patients. Patients with abnormal ECG have a more severe RV EAS involvement, which is proportional to the extent of T wave inversion across ECG 12-leads and a higher arrhythmic risk. The absence of negative T waves characterizes a low-risk subgroup of ARVC patients with a more favorable clinical course because of a low rate of arrhythmic events.

The results also showed that exercise-induced changes of negative T waves were unrelated to ARVC phenotypic manifestations and were of limited value for the differential diagnosis between ARVC and benign persistence of the juvenile repolarization pattern.

RIASSUNTO

Introduzione

La cardiomiopatia aritmogena del ventricolo destro (CAVD) è una patologia genetica del muscolo cardiaco caratterizzata da instabilità elettrica che può portare a aritmie ventricolari e morte improvvisa. Dal punto di vista patologico, la CAVD si caratterizza per una progressiva perdita di tessuto miocardico della parete libera del ventricolo destro (VD) con sostituzione fibro-adiposa. Il mapaggio elettroanatomico tridimensionale (*endocardial voltage mapping,* EVM) col sistema CARTO (Biosense-Webster, Diamond Bar, California) consente di identificare e caratterizzare aree di basso-voltaggio, dette "cicatrici elettroanatomiche" (CEA), che in pazienti affetti da CAVD corrispondono ad aree di sostituzione fibro-adiposa. Nonostante la tecnica abbia dimostrato di migliorare l'accuratezza per la diagnosi di CAVD, il suo valore per la stratificazione del rischio aritmico rimane da dimostrate. Inoltre, l'utilità dell'EVM per la quantificazione della cicatrice e la valutazione del rischio è limitata dalla natura invasiva, bassa disponibilità ed alti costi. Quindi, nella pratica clinica quotidiana è auspicabile la disponibilità di un esame non-invasivo, come l'elettrocardiogramma (ECG), per la stima dell'estensione della CEA e la stratificazione del rischio aritmico. Studi precedenti hanno dimostrato un'associazione tra la presenza di anomalie della ripolarizzazione o della depolarizzazione all'ECG e l'entità della dilatazione e della disfunzione del VD. In particolare, l'inversione delle onde T nelle derivazioni precordiali destre V1-V3 è uno dei segni distintivi della CAVD. Tuttavia, lo stesso segno ECG può essere riscontrato come "persistenza del pattern giovanile di ripolarizzazione" fino al 3% degli adulti sani. La prospettiva attuale è che le T negative persistano con l'esercizio nei pazienti con CAVD ma non nei soggetti sani. Tuttavia, questa idea non è supportata da dati scientifici.

Obbiettivo

L'obbiettivo dell'attività di ricerca è stato quello di caratterizzare ulteriormente alcune delle caratteristiche ECG della CAVD. Inizialmente, abbiamo valutato il valore prognostico della CEA all'EVM e la sua correlazione con vari esami non invasivi, in particolare l'ECG. In secondo luogo, abbiamo studiato le modificazioni indotte dall'esercizio nella T negative nelle derivazioni precordiali destre in un gruppo di pazienti con CAVD ed in un gruppo di soggetti sani con "persistenza del pattern giovanile di ripolarizzazione".

Metodi e risultati

Sono stati studiati 69 pazienti consecutivi affetti da CAVD (47 maschi, età mediana 35 [28-45] anni) che sono stati sottoposti a studio elettrofisiologico endocavitario con mappa di voltaggio unipolare e bipolare. L'estensione delle aree contenenti elettrogrammi di basso voltaggio bipolari (<1.5 mV) e/o unipolari (<6.0 mV) è stata stimata usando un software incorporato nel sistema CARTO. Cinquantatre pazienti (77%) mostravano ≥1 CEA con un'estensione pari a 24.8% (7.2–31.5) dell'estensione del VD alla mappa bipolare e del 64.8% (39.8–95.3) alla mappa unipolare (p=0.009). Nei rimanenti 16 pazienti con mappa bipolare normale, la mappa unipolare è risultata alterata con un'estensione delle lesioni pari al 26.2% (11.6–38.2) del VD. Nel corso di un follow-up medio di 41 (28-56) mesi, 19 (27.5%) pazienti hanno avuto un evento aritmico maggiore. All'analisi multivariata, l'unico predittore indipendente di eventi aritmici è risultata l'estensione della CEA alla mappa di voltaggio bipolare (hazard ratio=1.6 per 5%; intervallo di confidenza 95%: 1.2–1.9; P<0.001). I pazienti con mappa di voltaggio bipolare negativa hanno avuto un follow-up privo di eventi.

Successivamente, abbiamo analizzato un sottogruppo di 49 pazienti (38 maschi, età mediana 35 anni) con CAVD e mappa di voltaggio bipolare positiva. All'analisi univariata, la presenza di onde epsilon, il grado di dilatazione del VD, la severità della disfunzione del VD e l'estensione delle T negative all'ECG

correlavano con l'estensione della CEA alla mappa bipolare. All'analisi multivariata, l'estensione delle onde T negative è rimasta l'unico predittore di estensione della CEA (B=4.4, 95%CI 1.3-7.4, p=0.006). Questo parametro si è inoltre dimostrato correlare con il rischio di eventi aritmici durante il follow-up (p=0.03).

In una coorte differente, abbiamo valutato il comportamento durante test da sforzo delle T negative nelle derivazioni precordiali destre V1-V4 in 35 pazienti con CAVD (19 maschi, età media 22.2±6.2 anni) ed in 41 controlli appaiati per età e sesso con benigna "persistenza del pattern giovanile di ripolarizzazione". Al picco dell'esercizio, le onde T negative persistevano in 3 (9%) pazienti con CAVD, normalizzavano completamente in 12 (34%) e normalizzavano parzialmente in 20 (57%). I pazienti affetti da CAVD con e senza normalizzazione delle onde T durante l'esercizio mostravano un fenotipo simile. La prevalenza di normalizzazione (parziale o completa) delle onde T era simile nei pazienti e nei controlli (92% e 88%, p=1,0), mentre si è notato un trend non significativo verso una più alta prevalenza di normalizzazione completa nei controlli sani rispetto ai pazienti con CAVD (59% e 34%, p=0,06).

Conclusioni

In conclusione, i nostri risultati hanno mostrato che l'estensione della CEA bipolare alla mappa di voltaggio del VD è un potente predittore di rischio aritmico nei pazienti con CAVD, indipendentemente dalla storia aritmica e dal grado di disfunzione/dilatazione del VD. Una mappa di voltaggio bipolare normale caratterizza una popolazione di pazienti con CAVD a basso rischio. Abbiamo inoltre dimostrato che l'estensione della CEA bipolare può essere stimata dall'estensione delle anomalie della ripolarizzazione (T negative) all'ECG. I pazienti che non mostrano T negative all'ECG dimostrano un basso rischio aritmico. Infine, abbiamo dimostrato che il comportamento delle T negative nelle derivazioni precordiali destre V1-V3 non è un utile strumento di diagnosi differenziale tra CAVD e benigna "persistenza del pattern giovanile di ripolarizzazione".

INTRODUCTION

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic heart muscle disease characterized by electrical instability leading to ventricular arrhythmias and sudden cardiac death(1)(2). The hallmark pathological lesion of ARVC is the transmural loss of the myocardium of the right ventricular (RV) free wall with replacement by fibro-fatty tissue(3)(4). Three-dimensional electroanatomic voltage mapping (EVM) by CARTO system (Biosense-Webster, Diamond Bar, California) allows identification and characterization of low-voltage regions, i.e. "electroanatomical scars" (EAS)(5)(6)(7)(8), which in patients with ARVC correspond to areas of myocardial depletion and correlate with the histopathological finding of myocardial atrophy and fibro-fatty replacement at endomyocardial biopsy(9). EVM was proven to improve the accuracy for diagnosing ARVC in comparison to other diagnostic tests(8)(9). Although the technique has been demonstrated to enhance the accuracy for diagnosing ARVC, its value for arrhythmic risk stratification remains to be established. Furthermore, the clinical utility of EVM for scar quantification and risk assessment is limited by its invasive nature, low availability and high costs. Thus, in daily clinical practice there is the need of a non-invasive test for prediction of the amount of RV myocardial scar lesion and assessment of arrhythmic risk.

The electrocardiogram (ECG) is one of the oldest and most versatile non-invasive cardiac tests. It has remained in use essentially in its original form despite dramatic advances in cardiac electrophysiology. In May 1887, Augustus Desire´ Waller recorded the first human Electrogram using a primitive instrument called a Libbmann capillary electrometer. It had 2 deflections corresponding to ventricular depolarization and repolarization(10). In 1903, Willem Einthoven invented the String Galvanometer—a more sophisticated voltage recording instrument and recorded an Elektrokardiogramm with 5 deflections that he named PQRST(11). Surface 12-lead ECG has traditionally been an integral part of non-invasive

evaluation of ARVC patients. The ECG has an established clinical value for diagnosis of electrical abnormalities of ARVC, consisting of depolarization/repolarization changes and ventricular arrhythmias(12). Demonstration of late potentials on signal averaged ECG (SAECG) provides additional information on intraventricular conduction defect(13)(14)(15). Previous studies demonstrated an association between ECG repolarization/depolarization abnormalities and RV mechanical dilation/dysfunction in ARVC patients(14)(15)(16). It remains to be elucidated whether those ECG abnormalities correlate with the electrical consequences of fibro-fatty myocardial replacement, evidenced as EAS.

T wave inversion in right pericardial leads is the most common ECG abnormality of ARVC, present in up to 80% of ARVC patients(13)(14). However, the presence of T wave inversion in leads V1 to V2/V3, known as persistence of the juvenile pattern of repolarization, may also be observed in about 3% of healthy adults(17)(18)(19)(20)(21). The current perspective is that, at variance with healthy subjects, right precordial NTWs persist with exercise in ARVC patients. However, this view is not supported by systematic scientific data.

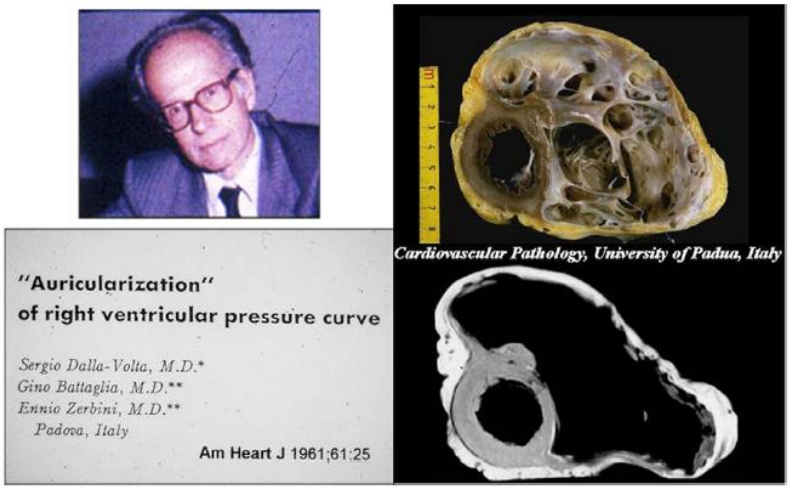
In this work, we aimed to further study some of the electrocardiographic features of ARVC. First, we assessed the prognostic value of electroanatomical scar (EAS) detected by endocardial voltage mapping and its correlation with various non-invasive characteristics of ARVC, including abnormalities detected by surface ECG. Second, we systematically studied the exercise-induced changes in right precordial negative T waves in patients with ARVC.

Historical background

Giovanni Maria Lancisi (1654-1720) was an anatomist, clinician, epidemiologist, advisor to Pope Clement XI and one of the greatest Italian physicians of the first half of the 18th century (Figure 1). In his book, De Motu Cordis et Aneurysmatibus, Lancisi reported a four generation family with sudden deaths and dilatation and aneurysms of the right ventricle(22). Two hundred and thirty years later, the University of Padua set the first milestone for the modern description of ARVC, as in 1961 and 1965 Sergio Della Volta first reported cases with "auricularization of the RV pressure" in which he described a series of patients with RV chamber with no effective systolic contraction, with the blood being pushed to the pulmonary artery mainly due to the right atrial systole(23)(24). Although the patients presented also with ventricular arrhythmias, Della Volta focused more on the hemodynamic features of the cases. One of the original patients reported by Della Volta underwent cardiac transplantation 30 years later in 1995 at the age of 65 because of congestive RV failure. The left ventricle was normal, whereas the RV was hugely dilated with diffuse paper-thin free wall and complete disappearance of the myocardium (figure 2) (25). In 1982, Dr. Frank Marcus (University of Arizona, United States) collaborating with a French group of researchers described the disease of right ventricular dysplasia in a series of 24 patients referred to La Salpetrière Hospital and Jean Restand Hospital in Paris from 1973 to 1980. The group characterized some of the fundamental clinical elements of the disease including the T wave inversion in the right precordial leads on the surface electrocardiogram (ECG), the left bundle branch block pattern of the QRS complex during spontaneous ventricular tachycardia, and the echocardiographic features of normal left ventricle with enlarged and aneurismal right ventricle(26). In 1986, Protonotarios et al, studied nine cases of palmoplantar keratosis in the Greek island of Naxos, of which seven showed symptoms and signs of heart disease. Three cases had episodes of ventricular tachycardia (VT) and a fourth patient died suddenly.

Figure 1. Giovanni Maria Lancisi (1654-1720), was an Italian physician, epidemiologist and anatomist. He observed marked neck venous pulsations with tricuspid valve insufficiency (later to be known as Lancisi's sign) and associated aortic arch aneurysms with syphilis in his masterpiece in cardiac pathology; *De Motu Cordis et Aneurysmatibus* (On the motion of the heart and on aneurysms) which was published posthumously in 1738. In this book also he reported the first known family of sudden cardiac death and right ventricular aneurysms.

Figure 2. Professor Sergio Dalla Volta, the title of his original article, and the cardiac specimen at transplantation of one of his patients. Source: Thiene G. "Arrhythmogenic ardiomyopathy: from autopsy to genes and transgenic mice (SCVP Achievement Award Lecture, San Antonio, TX)



All patients with cardiac signs and symptoms showed echocardiographic enlargement of the right ventricle and a right ventricular band. Moreover, the left ventricle was also affected in 3 patients(27). The described cardiocutaneous syndrome, coined as “Naxos disease”, is an autosomal recessive form of ARVC (figure 3). The current concept of the clinical and pathological picture of ARVC was again established in the University of Padua. Familial occurrence of ARVC with autosomal dominant pattern and incomplete penetrance was proven by Nava, et al. in 1988(28). Furthermore, Thiene et al. associated the pathology of ARVC with a series of SCD in the (≤35 years), mostly during effort. All the cases had T wave inversion on the right precordial surface ECG at rest and left bundle branch block QRS pattern during the ventricular tachycardia(1). This was the first time ARVC was acknowledged as a major cause of death in the young.

Incidence

ARVC incidence is estimated to be 1 in 2,500 to 5,000 in the general population with male predominance(2). It is considered one of the major causes of sudden cardiac death (SCD) in the young and young athletes(1). Athletes affected with ARVC represent a specially high risk of SCD group(29).

ARVC had been traditionally associated with the Mediterranean region, as many seminal studies had originated from research groups in France, Greece, and Italy. Today, however, numerous ARVC registries from all over the world emphasize that the disease does not have a specific racial or geographical predilection (figure 4) (30).

Pathology

The pathological diagnosis of ARVC has been traditionally based on the gross and histological evidence of transmural myocardial loss with fibrofatty replacement of the right ventricle (RV) free wall,

extending from the epicardium toward the endocardium(1). Gross morphological findings of ARVC include focal areas of severe muscle thinning –that may transillimunate under a light source-, local or global ventricular cavity enlargement, and ventricular wall aneurysms. Aneurysms are only present in 20 to 50% of autopsy cases of ARVC(31)(4). RV aneurysms, located in the triangle of dysplasia (inflow, apex, outflow tract) are considered pathognomonic for ARVC(26). However, autoptic features of ARVC may range from grossly normal hearts, in which only a careful histopathological investigation can reveal ARVC features, up to massive RV and/or LV involvement.

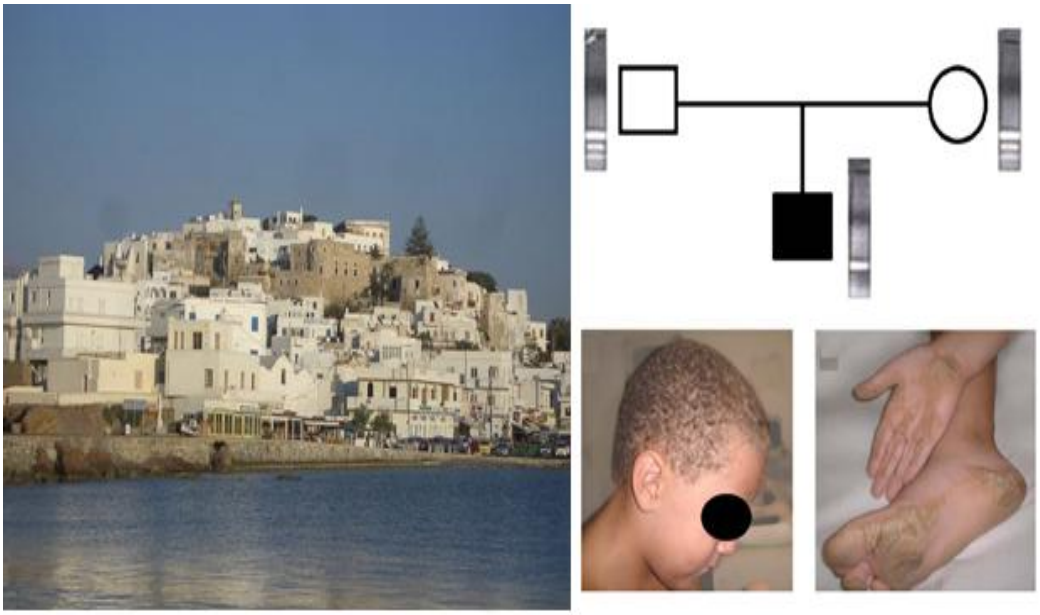


Figure 3. Clockwise from left: The Greek island of Naxos. A nuclear Naxos disease family. Analysis reveals the presence of mutant allele (one bold band) in the homozygous boy and the wild-type (two light bands) coexisting with the mutant one in the heterozygous carrier parents. Keratoderma striate in palmar and diffuse in plantar areas in the homozygous boy. Wooly hair.

Source: Protonotarios N and Tsatsopoulou A, 'Naxos Disease and Carvajal Syndrome: Cardiocutaneous Disorders That Highlight the Pathogenesis and Broaden the Spectrum of Arrhythmogenic Right Ventricular Cardiomyopathy.', *Cardiovascular pathology*, 13 (2004), 185–94.

Figure 4. The global perspective of ARVC: ARVC has been reported and studied in Europe, Middle East, South Africa, India, China, Japan, Australia, North America and South America.

Source: Elmaghawry M, et al., 'A Global Perspective of Arrhythmogenic Right Ventricular Cardiomyopathy.', *Global cardiology science & practice*, 2012 (2012), 81–92.

Therefore, the existence of cases with biventricular involvement or predominantly with LV or RV involvement suggest the use of the more comprehensive term arrhythmogenic cardiomyopathy (AC) instead of the limiting ARVC (32) (33).

Histological examination reveals islands of surviving myocytes interspersed within fibrous and fatty tissue. Clusters of dying myocytes provide evidence of the acquired nature of myocardial atrophy, and are frequently associated with inflammatory infiltrates (figure 5) (32). Rather than being a continuous process, disease progression may occur during periodic bursts. Environmental factors, such as exercise or inflammation, may facilitate onset and progression of myocyte loss and fibrofatty replacement(34). The deposition of adipose tissue is a peculiarity of ARVC, however its specificity has been controversial.

Significant fat infiltration of the RV is reported in more than 50% of normal hearts in the elderly(35). It has been recently suggested that isolated adipose replacement of the RV myocardium should only be considered pathological if observed in association with myocytes at various stages of cell death(36).

Figure 5. Arrhythmic cardiomyopathy pathology. A: Cross section of a heart of a 17 year old male who died suddenly during a football match. Note the right ventricular dilatation, fibro-fatty replacement and anterior and posterior wall aneurysms. B: Histology of the right ventricular free wall of the same patient showing transmural fibrofatty replacement. C: Histology of the left ventricular free wall showing focal subepicardial left ventricular involvement.

Source: Thiene G, Corrado D, Basso C, 'Arrhythmogenic Right Ventricular Cardiomyopathy/dysplasia.', *Orphanet journal of rare diseases*, 2 (2007), 45.

Pathogenesis

Many theories have been postulated to explain the mechanism of the loss of the ventricular myocardium and its substitution by fibrous and fatty tissue: dysplasia, myocarditis, transdifferentiation,

and dystrophy. The original concept of the disease as congenital abnormality (dysplasia, aplasia, or hypoplasia) characterized with maldevelopment of RV myocardium(26). This led to the historical confusion in literature between ARVC and Uhl's anomaly. Henry Uhl, at the Johns Hopkins Hospital in Baltimore, in 1952, reported a case of an almost total absence of the myocardium of the RV in a 7-month-old infant, with the epicardium and endocardium lie adjacent to each other with no intervening cardiac muscle and no fibrofatty tissue observed in the RV free wall(37). On the contrary in ARVC, myocardial death occurs after birth, usually during childhood, and is progressive with time. Another theory was the inflammatory process; with myocardial loss due to infective or immune mechanisms. Cardiotropic viruses, such as adenovirus, hepatits C virus, and parvovirus B19, have been reported in the myocardium of some AC patients(38). However, the viral agent might be just an innocent bystander or play a secondary role to the progression of myocardial loss. Transdifferentiation of myocytes into fibrocytes and/or adipocytes has also been proposed(39). This theory is questionable because of the limited de-differentiaton capabilities of adult cardiomyocytes. Myocyte dystrophy remains the most likely explanation to the ARVC pathological process. Similar to skeletal muscle dystrophy observed in Duchenne or Becker diseases, a progressive and acquired myocardial atrophy with replacement by exuberant fatty and fibrous tissue occurs in the hearts of ARVC patients. This dystrophy, either by apoptosis or necrosis, could account for a genetically determined loss of myocardium(4)(34)(40).Transgenic animal models have been recently developed, supporting the dystrophy theory. A transgenic mouse with cardiac-restricted overexpression of the C-terminal mutant (R2834H) desmoplakin has been shown to develop increased cardiomyocte apoptosis, myocardial fibrosis, and lipid accumulation as well as biventricular dilatation/dysfunction(41). In another seminal study of a transgenic mouse model (Tg-NS) with cardiac overexpression of desmoglein-2 gene mutation N271S, clinical features of AC, as well as, myocyte necrosis were obsereved in all Tg-NS hearts(42).

Role of Desmosomes in Arrhythmic Cardiomyopathy Pathogenesis

Desmosomes are a specific type of cell junction within intercalated discs, the specialized intercellular junctions of cardiomyocytes (Figure 6). They form membrane anchorage sites for intermediate filaments, and the resulting complex is thought to impart tensile strength and resilience. The cardiac desmosomes have been proposed to support structural stability through cell-cell adhesion, to regulate adipogenesis and apoptosis related genes, and to maintain proper electrical conductivity through the regulation of gap junctions and Ca^{2+} homeostasis. Functionally, desmin forms intermediate filaments in mature striated muscle that surround the Z discs and link the entire contractile apparatus to the sarcolemmal cytoskeleton, cytoplasmic organelles and nucleus. Desmoplakin (DSP) and junctional plakoglobin (JUP) are constituents of the submembranous plaques of the desmosomes, along with plakophillin (PKP), and they form part of the link between the intermediate filament cytoskeleton and the cytoplasmic tail of cadherins. The desmosomal cadherins are calcium-dependent cell adhesion glycoproteins, divided in two classes namely, the desmoglein (DSG) and the desmocollin (DSC), and they mediate lateral and transcellular desmosomal adhesion (Figure 6&7).

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

regardless of the extent of myocyte loss. For example, it has been recently demonstrated that PKP2 associates with sodium voltage gated channels Na(V)1.5, and that knockdown of PKP2 expression alters the properties of the sodium current, and the velocity of action potential propagation in cultured cardiomyocytes(43).

Heritability

ARVC cases have been shown to have a genetic component, with approximately one-third to one-half of them being familial. The inheritance pattern is autosomal dominant, i.e. both mutation homozygotes as well as heterozygotes can develop ARVC, although rare autosomal recessive cases – where only mutation homozygotes can present with the disease – have also been reported(44). ARVC causing mutations have variable expressivity, with highly variable phenotypes, ranging from severe disease with early death to individuals who were completely asymptomatic late in life, even among family members carrying the same gene mutation(45)(46).

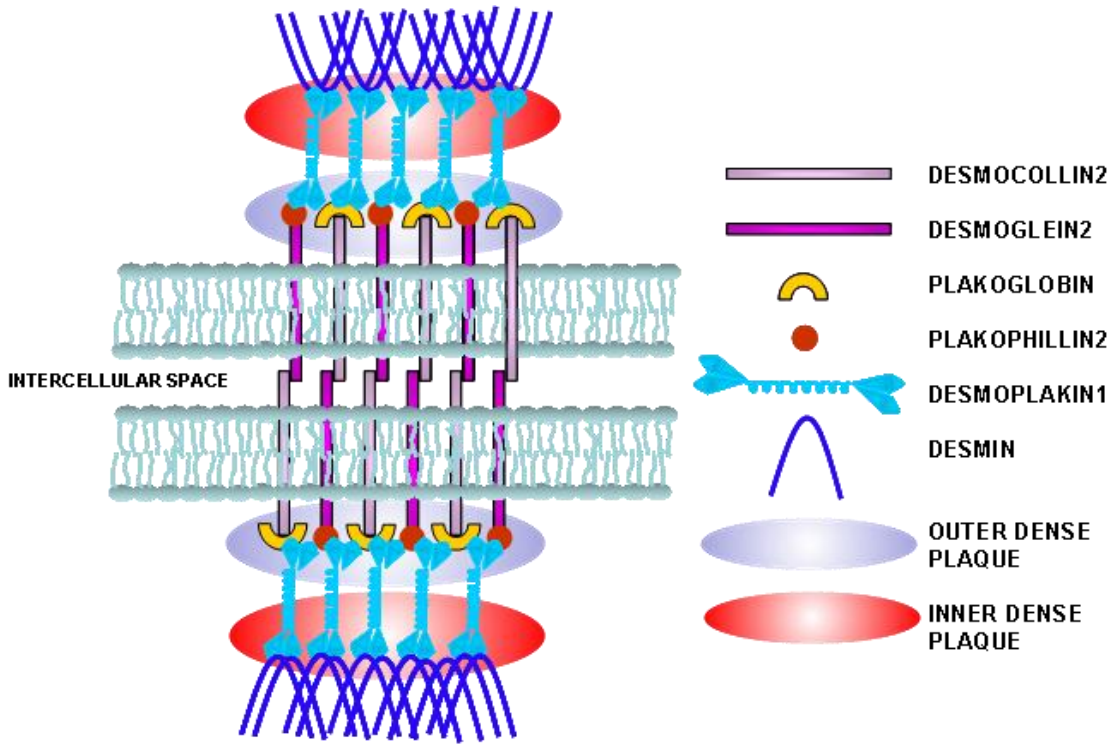


Figure 6. The desmosome consists of three families of proteins: the desmosomal cadherins, desmocollin and desmoglein, members of the armadillo family of proteins, plakoglobin and plakophillin and the plakins. Binding of these proteins tethers desmin intermediate filaments to the plasma membrane in cardiac myocytes and adheres adjacent myocytes together.

Source: Elmaghawry M, et al., 'Science and Practice of Arrhythmogenic Cardiomyopathy: A Paradigm Shift.', *Global cardiology science & practice*, 2013 (2013), 63–79.

Penetrance is incomplete (20-30% or higher), with a significant percentage of the mutation carriers not presenting with an unaffected, normal phenotype(47). Interestingly, gender may have an influence on penetrance, with male mutation carriers more likely to develop specific phenotypic manifestations of this disease(31). The reduced penetrance along with variable expressivity, suggest that other genetic modifiers and/or environmental factors are implicated in disease pathogenesis. At the genetic counseling level, these

characteristics make it difficult to trace the disease along a family line and to identify the members at risk of carrying a mutation.

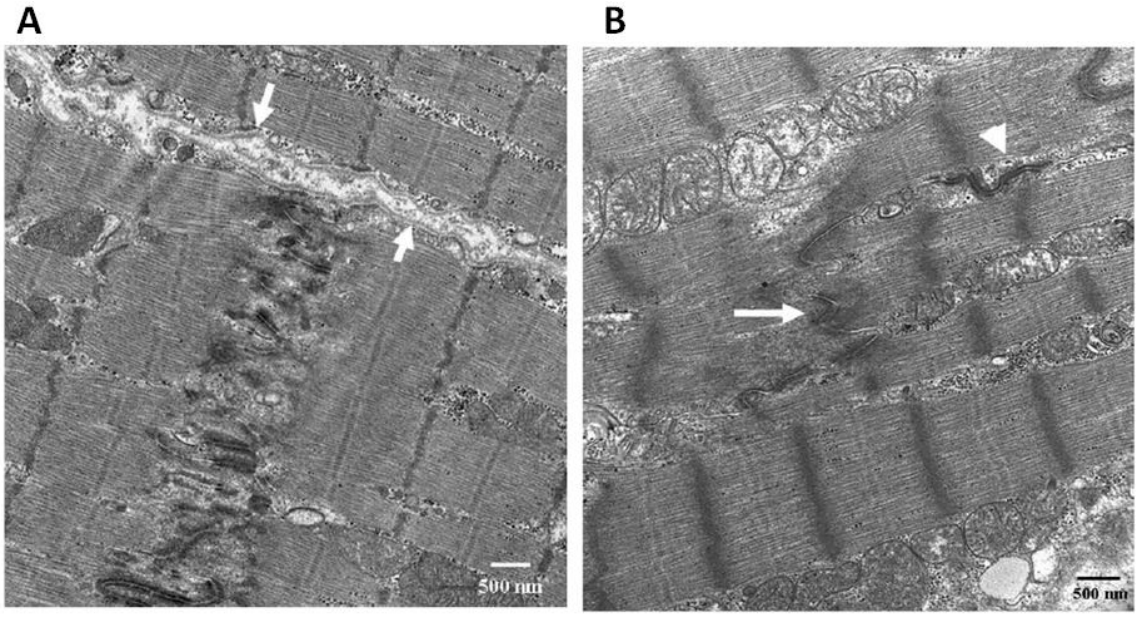


Figure 7. Electron microscopic view of cardiac myocyte intercalated discs. **(A)** Normal case control. Regular cell membrane (arrows) and intercalated disc between adjacent myocytes. **(B)** ARVC patient with desmoplakin gene splice site mutation . Note the abnormal position of long desmosomes (arrowhead) and the widened gap of facia adherens (arrow). Original magnification: X15 000.

Source: Basso C, et al., 'Ultrastructural Evidence of Intercalated Disc Remodelling in Arrhythmogenic Right Ventricular Cardiomyopathy: An Electron Microscopy Investigation on Endomyocardial Biopsies.', *European heart journal*, 27 (2006), 1847–54.

Genetics

AC causative mutations have been identified in ten different genes, although two of these (TGFB3 and RYR2) are currently rarely associated with AC. Four additional genes associated with

autosomal dominant arrhythmogenic right ventricular dysplasia (ARVD) have been mapped but not identified (locus names ARVD3, ARVD4, ARVD6, and ARVD7). Molecular genetic testing is clinically available for eight of the ten known genes (Table 1). Since ARVC is emerging a desmosome related disease (8 of 10 genes are desmosome related), desmosome gene mutations accounting for approximately 50% of symptomatic individuals(48), and compound and digenic heterozygosity being often encountered, screening of all desmosomal ARVC related genes is now recommended(49). Among the different desmosome genes, mutations have been identified in desmoplakin (DSP), plakophilin-2 (PKP-2), desmoglein-2 (DSG-2), desmocollin-2 (DSC-2), junction plakoglobin (or gamma catenin) (JUP), and more recently in plakophilin-4 and desmin(50).

Of note, mutations in some of these genes have been associated with genetically related (allelic) disorders. Specifically, RYR2 mutations have been identified in individuals with catecholaminergic polymorphic ventricular tachycardia (CPVT)(51)(52), as well as patients with "atypical" or "borderline" long QT syndrome (LQTS) who did not have mutations identified in the five genes associated with LQTS(53). DSP mutations can lead to Carvajal syndrome, an autosomal recessive disease characterized by ventricular dilated cardiomyopathy associated with keratoderma and woolly hair (54)(55)(56) (figure 8), while JUP mutations can be causative of Naxos disease, an autosomal recessive form of ARVC characterized by palmoplantar keratoderma and peculiar woolly hair that was first observed on the island of Naxos, Greece(57). Historically, it was the phenotype of woolly hair and palmoplantar keratoderma in those two syndromes that pointed scientists towards screening desmosomal genes for pathogenetic mutations. Interestingly, as opposed to other ARVC subgroups, Naxos disease has full penetrance by adolescence(58).

Ongoing efforts are aiming to identify genotype-phenotype correlations, with interesting preliminary. For example, compared with those without a desmosome gene mutation, individuals with a desmosome gene mutation had earlier-onset AC and were more likely to have ventricular tachycardia(59). Recent studies have also suggested that for rare desmosome gene mutations (namely, *DSG2* and *DSC2*), the presence of

multiple mutations simultaneously may be required to manifest the ARVC phenotype and may be associated with increased disease severity, namely higher frequency of sudden death (60).

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

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

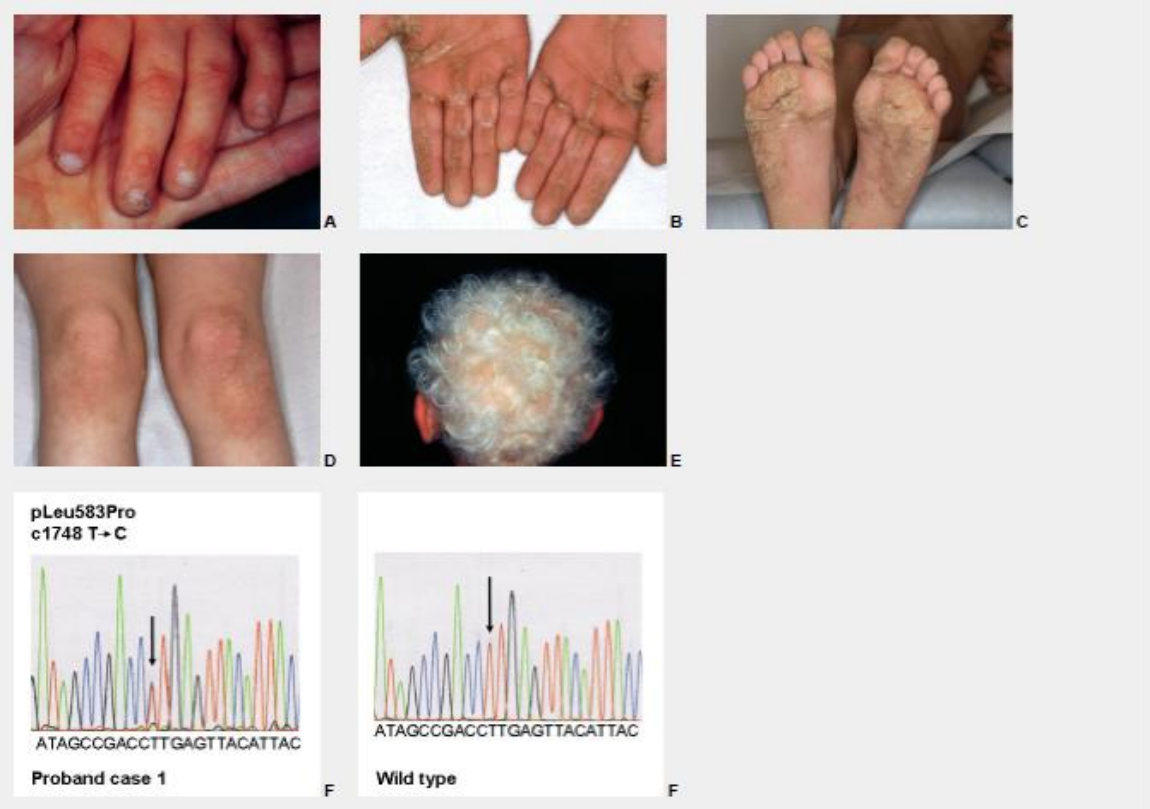


Figure 8. Deramological phenotype and genetic screening of a case of Cardiocutaenous syndrome (Carvajal). **(A)** Dystrophic nail plates. **(B)** Striate keratoderma of the palms. **(C)** Plantar keratoderma. **(D)** Erythemato-squamous skin lesions of the knee. **(E)** curly wooly hair. **(F)** Electropherograms of the desmoplakin mutation and of the wild type: a heterozygous variant in DSP, c.1748 T>C, was identified, resulting in the missense mutation p.Leu583Pro at a heterozygous state.

Source: Keller D, et al,, 'De Novo Heterozygous Desmoplakin Mutations Leading to Naxos-Carvajal Disease.', *Swiss medical weekly*, 142 (2012).

Clinical Picture and task Force Criteria

Clinically, the patient usually presents with palpitations, due to premature ventricular complexes (PVCs) or nonsustained ventricular tachycardia. Other presentations are sustained ventricular tachycardia, syncope, resuscitated cardiac arrest, right heart failure or late stage biventricular heart failure(2). Multiple criteria are needed to diagnose ARVC, as there is no single gold standard criterion sufficiently specific to establish the diagnosis(58). Even the presence of desmosomal genetic abnormality is not sufficient as there is variable penetrance. However, it is important to note that the recessive form of ARVC (Naxos disease) presents full penetrance by adolescence, being associated with cutaneous abnormalities consisting of woolly hair and palmoplantar keratoderma(61). This diagnostic challenge led to the formation of an expert Task Force that in 1994 proposed major and minor criteria to aid in the diagnosis(62). The report achieved its goal of standardizing diagnostic criteria. With the growing International experience, an updated modified Task Force criteria (TFC) were published in 2010(11). The modified criteria include structural alterations observed by echocardiogram, cardiac magnetic resonance imaging and/or angiography. They also include tissue characterization of RV wall, repolarization abnormalities, depolarization abnormalities, arrhythmias, and family history (table 2). The modified criteria are also based on more quantitative analysis rather than the 1994 TFC qualitative nature.

Table 2. Revised 2010 Task Force critiria for diagnosis of ARVC. Source: Marcus F, et al., 'Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy/dysplasia: Proposed Modification of the Task Force Criteria.', *European heart journal*, 31 (2010), 806–14.

1- Endomyocardial biopsy
Major: • *The total amount of the residual myocytes is less than 60% by morphometric analysis (or less than 50% if estimated), and the remaining of the free wall myocardium is replaced by fibrous tissue with or without fatty changes in more than one sample.*

Minor :

- *The total amount of the residual myocytes is 60% to 75% by morphometric analysis (or 50% to 65% if estimated), and the remaining of the free wall myocardium is replaced by fibrous tissue with or without fatty changes in more than one sample.*

2-Right ventricular structural and functional abnormalities

A- Echocardiography

Major :

- *Regional wall akinesia, dyskinesia, or aneurismal dilatation of the RV*

  Plus one of the following:

  1) Right ventricular outflow tract of 19 mm/m2 in parasternal long axis view at the end diastole, 21 mm/m2 in parasternal short axis view at the end diastole

  2) RV fractional area change <33%.

Minor :

- *Regional wall akinesia or dyskinesia*

  Plus one of the following :

  1) Right ventricular out flow tract of 16 to19 mm/m2 in parasternal short axis view at the end diastole or 18 to 21 mm/m2 in parasternal short axis view at the end diastole

  2) RV fractional area change 33-40%.

B- Cardiac magnetic resonance

Major :

- *Regional wall akinesia or dyskinesia or dyssynchronous contraction*

  Plus one of the following:

  1) Ejection fraction less than 40%,

  2) End-diastolic volume t more than 110 mL/m2 ,or more 100 mL/m2 in males and females, respectively.

Minor :

- *Regional wall akinesia or dyskinesia or dyssynchronous contraction*

  plus one of the following*:*

  1) Ejection fraction less than 40%,

  2) End-diastolic volume t more than 110 mL/m2 ,or more 100 mL/m2 in males and females, respectively.

B- Right ventricular angiography

Major :

- *≥1 diskinetic, akinetic or aneurismatic right ventricular regions*

3- Electrocardiographic repolarization abnormalities

Major :-

- *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).*

Minor :-

- *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.*

4-Electrocardiographic depolarization abnormalities

Major :

- *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).*

Minor :

- *Late potentials by Signal Avereged ECG in >1 of 3 parameters in the absence of a QRS duration of >110 ms on the standard ECG:*
    1) *Filtered QRS duration (fQRS) >114 ms.*
    2) *Duration of terminal QRS ,40 mV (low-amplitude signal duration) >38 ms*
    3) *Root-mean-square voltage of terminal 40 ms <20 mV*
- *Terminal activation duration of QRS >55 ms measured from the nadir of the S wave to the end of the QRS, including R0, in V1, V2, or V3, in the absence of complete right bundle-branch block.*

5- Arrhythmias

Major :

- *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).*

Minor :

- *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 premature ventricular beats per 24 hours (Holter).*

6. Family history/genetics

Major :

- *Positive family history of first-degree relative confirmed by current task force criteria.*
- *Pathological confirmation of the disease in first-degree relative either by autopsy or surgery.*
- *Discovering of a DNA pathogenic mutation that has been recognized to be associated or probably associated with ARVC in the patient who has been evaluated for ARVC.*

Minor:

- *Positive family history of first-degree relative in whom the diagnosis is not feasible to be confirmed by current Task Force criteria.*
- *Positive family history of young (<35 years) first degree relative with sudden death due to suspected ARVC.*
- *Positive family history of disease in second degree relative who has been confirmed to have the disease either by current Task Force Criteria or pathologically.*

Diagnosis

Established: At least two major criteria, one major criteria and three minor criteria, or four minor criteria from different categories

Borderline: One major criteria and two minor criteria, or three minor criteria from different categories

Possible: One major criteria or two minor criteria from different categories

Electrocardiogram

The 12-lead electrocardiogram (ECG) is one of the most important tools for the diagnosis, follow-up and SCD risk stratification of AC (figure 9). Depolarization abnormalities due to activation delay as a result of cellular uncoupling and fibrofatty alteration include the epsilon wave, widening of the QRS complex (>110 msec) in leads V_1 to V_3 and evidence of late potentials by signal averaged ECG (SAECG). Epsilon wave is a defined as reproducible low amplitude signals between the end of the QRS complex to the onset of the T wave in the right precordial leads (V_{1-3}). Although the epsilon wave is very specific for ARVC, Cox et al, showed that this parameter had a very low sensitivity (10%). Widening of the QRS complex was a criterion in 1994 TFC, but it was deleted in the 2010 TFC due to possible confusion especially in the presence of a right bundle branch block (RBBB). To overcome this confusion, many studies have proposed new ECG markers that focus on delayed RV activation in precordial leads. These include the presence of partial block(63), delayed S wave upstroke in $V_{1-3} \geq 55$ msec(64), increased ratio of QRS duration in the right versus the left precordial leads(65), and a prolonged terminal activation duration ≥55 msec(66). Right precordial QRS prolongation and QRS dispersion have been significantly associated with an increase of the arrhythmic risk in patients with AC. In an important study, Turrini et al., showed a greater QRS prolongation (125 msec) in V1 to V2/V3 in AC patients with SCD, in comparison with living ARVC patients (113 msec). They also demonstrated that QRS dispersion of more than 40 msec (between the longest and shortest QRS intervals) was a strong predictor of SCD in ARVC(67). Abnormalities in repolarization in ARVC are represented as inverted T wave. Due to its high sensitivity, inverted T waves in V1-V3 or beyond in the absence of RBBB and in >12 year old individuals was upgraded from a minor criterion in the 1994 TFC to a major criterion in the 2010 TFC, for individuals older than 14 years and in absence of complete RBBB(11). The morphology of recorded ventricular tachycardia (VT) reflects its site of origin. In ARVC, affected areas in the triangle of dysplasia usually produce a VT with a left bundle branch block morphology and a superior axis, defined from -30^o to -150^o. Because of the variable extension of the disease, multiple VT morphologies are usually recorded

in a single patient. Studies showed the mean number of different VT morphologies per patient ranges from 1.8 to 3.8(68)(69).

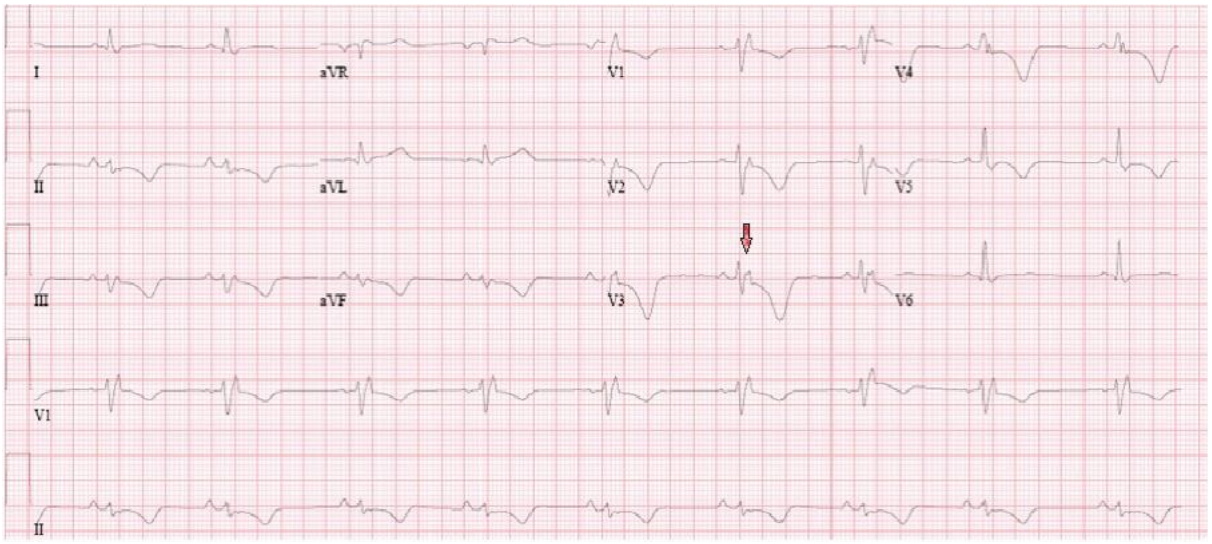


Figure 9. 12 Lead ECG of arrhythmogenic cardiomyopathy. Note the "epsilon wave" in V_3, the right pericardial leads localized QRS prolongation which is mainly due to a terminal activation delay (from nadir of S to the end of QRS complex), and T wave inversion in V_{1-3}.

Echocardiography

Echocardiography is of paramount importance in the initial evaluation and follow up of ARVC patients because of its availability, ease of performance and interpretation, cost effectiveness and non invasive advantages (figure 10)(70). The multidisciplinary Study of Right Ventricular Dysplasia demonstrated that the diagnostic performance of transthoracic echocardiography was superior to MRI with 80% accuracy in affected individuals with AC and 40% accuracy in borderline individuals, compared with 49% and 15% for MRI, respectively (71)(72). RV outflow tract dilatation (in parasternal long axis view >32 mm or in parasternal short axis view >36 mm) coupled with localized anuerysms

(akinesia or dyskinesia) or global dysfunction (fractional area change <33%) is now considered a major criterion for the diagnosis of ARVC(11). Other echocardiographic features to assess RV anatomic alteration include the ratio between the RVOT/aorta in parasternal short axis view (abnormal if >1.2), longitudinal and transverse RV axes in apical four chamber and subcostal views, visualization of RV apical trabeculation in the subcostal view. Emerging echocardiographic techniques being currently evaluated include 3 dimensional echocardiography(73), RV free wall myocardial velocity, strain and strain rate by Doppler or speckle tracking (figure 11)(74)(75).

Right Ventriculography

RV ventriculography remains an integral imaging modality and reference technique in the diagnosis and evaluation of patients with ARVC. This technique should be performed in all patients with suspected or definite ARVC and may be combined with electrophysiological study and/or RV endomyocardial biopsy. The angiographic diagnosis of ARVC is based on segmental abnormalities rather than diffuse RV enlargement or hypokinesia. Dedicated computer softwares for the evaluation of RV volume and regional wall motion have been developed and provide a convenient and reproducible method for quantitative assessment of global and regional RV contraction and relaxation(76)(77).

Magnetic Resonance Imaging

Among the current cardiac magnetic resonance imaging (MRI) applications in cardiomyopathies, the greatest potentials and challenges are in the diagnosis of ARVC. Routinely used imaging planes are suboptimal for RV evaluation, and the technique of ARVC imaging involves unconventional imaging planes. Furthermore, the lack of familiarity of the MRI interpreters with RV contraction pattern and the normal epicardial fat distribution pose challenges for accurate and reproducible reporting.

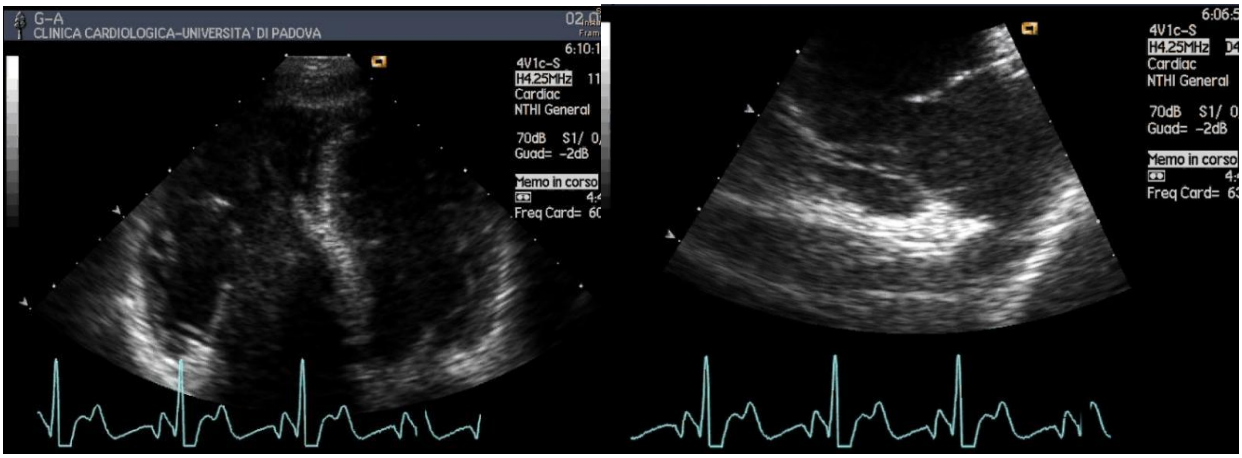


Figure 10. Echocardiography of a patient with arrhythmic cardiomyopathy. Upper panel shows an apical 4 chamber view with dilated anuerysmal right ventricle. Lower panel shows a modified short axis left paraternal view to visualize the subtricuspid area which shows a localized aneurysm.

(Images courtesy of MP Marra, MD, University of Padua, Italy).

Also, it requires a high degree of expertise to accurately differentiate ARVC from alternative diseases with similar MRI picture -especially late gadolinium enhancement (LGE)- such as myocarditis and sarcoidosis(78). Finally, over-reliance on the presence of intramyocardial fat has resulted in a high frequency of misdiagnosis of ARVC(79). Despite of these limitations, cardiac MRI has emerged as a robust tool to evaluate ARVC patients (figure 12). It has the ability to noninvasively provide tissue characterization for detection of fat and more importantly fibrosis in the RV, and also the LV. Quantitative data on ventricular volumes, functions, and regional contraction abnormalities are useful in the diagnosis and follow up of patients with ARVC(80). MRI studies have also helped in genotype-phenotype correlation of ARVC; LV involvement is rare in PKP 2 mutation but more common in desmoplakin and plakoglobin mutation carriers(33)(81).

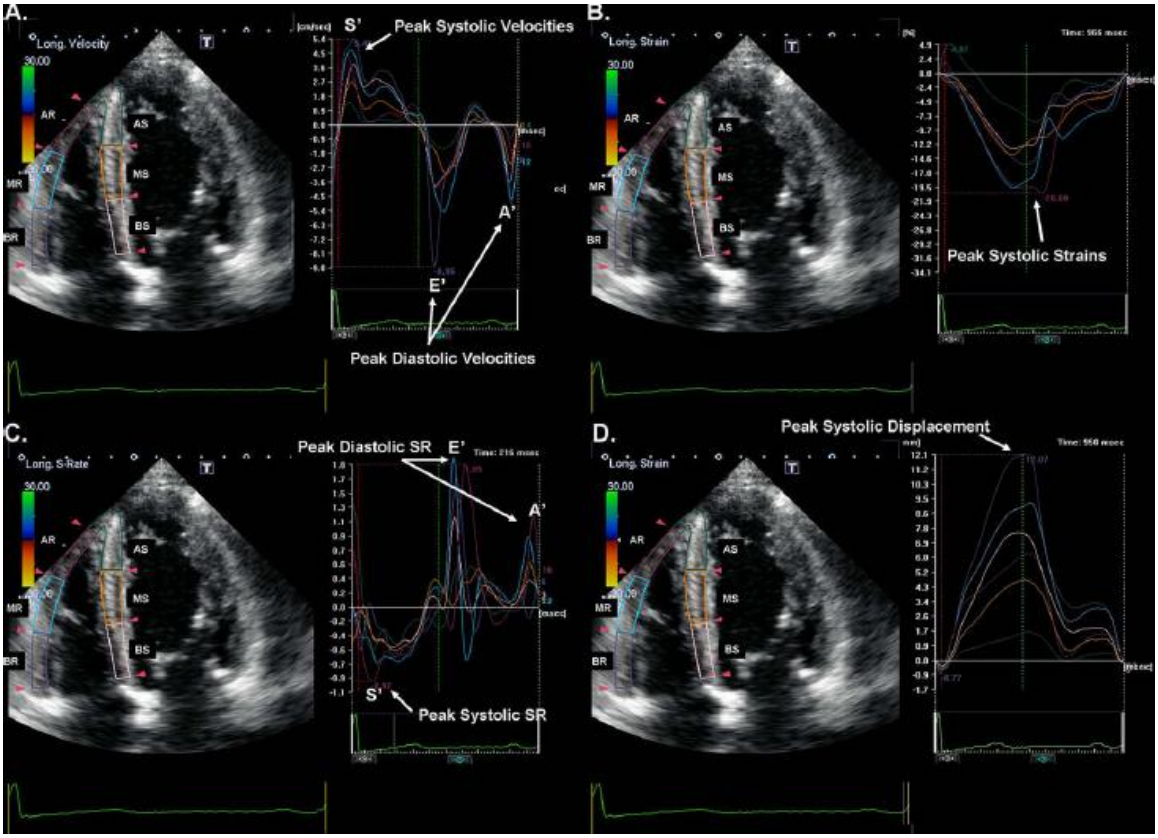


Figure 11. Apical 4-chamber view with 2D speckle imaging of the LV septum and RV free wall in a normal older patient. The images display longitudinal velocity **(A)**, strain **(B)**, strain rate (SR) **(C)**, and displacement **(D)** curves. A', Late diastolic waveform; AR, apical right ventricle; AS, apical septum; BR, basal right ventricle; BS, basal septum; E', early diastolic waveform; MR, mid right ventricle; MS, mid septum; S', systolic waveform.

Source: Horton K, Meece R, Hill R, 'Assessment of the Right Ventricle by Echocardiography: a Primer for Cardiac Sonographers.', *Journal of the American Society of Echocardiography*, 22 (2009), 776–92.

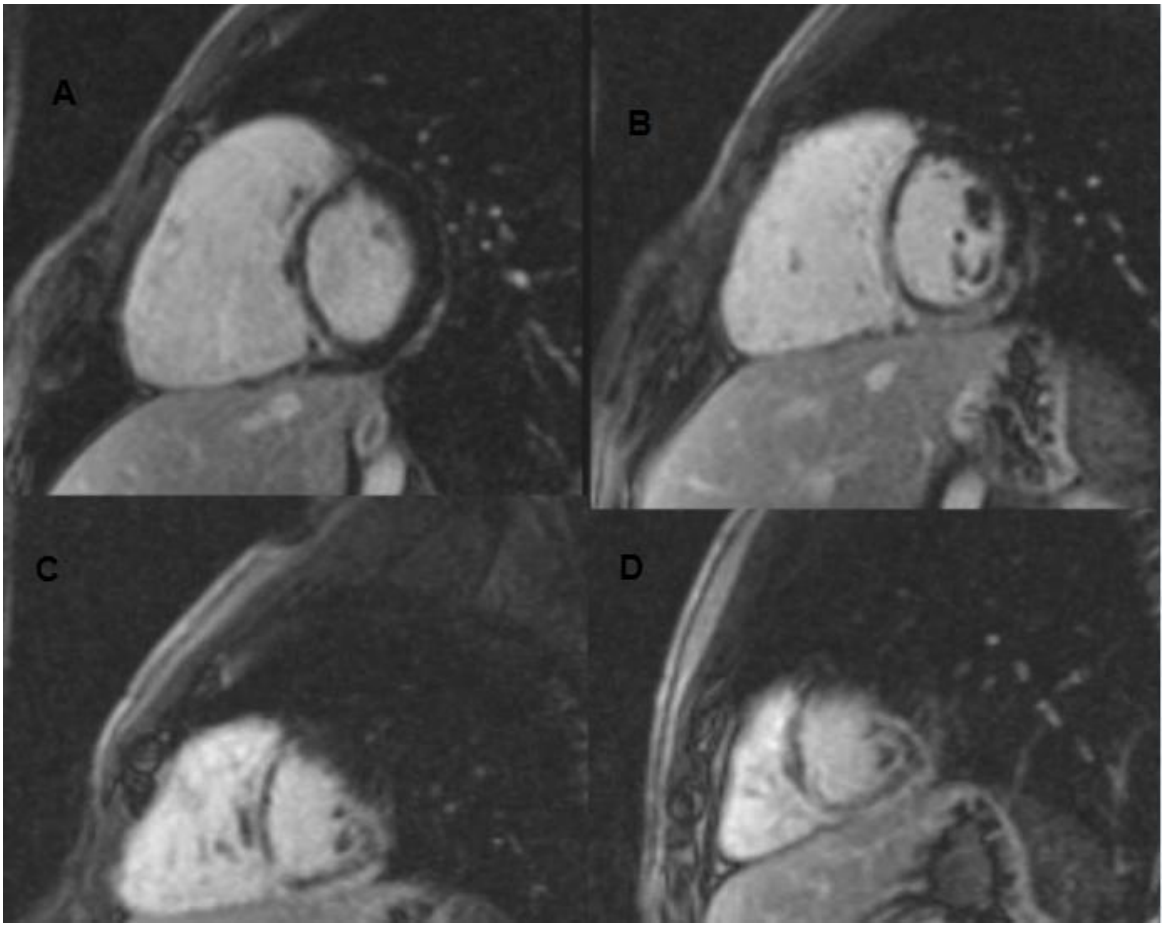


Figure 12. Cardiac magnetic resonance imaging of a patient with extensive AC. Short axis view from base (upper left) to apex (lower right) demonstrating extensive fibrosis as evidenced by delayed gadolinium enhancement in most of right ventricular wall (only sparing a small infero-septal area), interventricular septum and the epicardium of the left ventricular inferior wall. This patient underwent cardiac transplantation for severe right heart failure. (Images courtesy of MP Marra, MD, University of Padua, Italy)

Electrophysiological mapping and Ablation

Three dimensional electro-anatomic mapping has helped in understanding the substrate and mechanisms underlying VT in ARVC patients. Electrical activation through normal RV myocardium was

defined in patients with no structural heart disease with the use of the CARTO electro-anatomic mapping system and the Navistar catheter (Biosense Webster, Diamond Bar, CA, USA), which has a 4-mm distal tip electrode, and a 1-mm inter-electrode distance. Normal RV endocardium is characterized by bipolar signals displaying 3 or fewer deflections from baseline, with peak to peak amplitude greater than 1.5 mV, whereas areas of bipolar voltage less than 0.5 mV correspond to dense scar, i.e., EAS. RV bipolar EAS was demonstrated to correlate with the histopathologic finding of fibrofatty myocardial replacement at endomyocardial biopsy in AC patients(8)(9). Corrado and colleagues demonstrated that electrovoltage mapping enhances the diagnostic specificity of ARVC by distinguishing between pure genetically-determined ARVC, which is characteristically associated with EAS involvement, and acquired RV inflammatory cardiomyopathy, mimicking AC but showing a preserved electrogram voltage and a better prognosis(8)(9). Moreover, electrovoltage mapping has been proven to increase diagnostic sensitivity for early/minor form of AC underlying apparently idiopathic RVOT tachycardias, by detecting otherwise concealed segmental RV EAS areas in the RVOT, which are associated with a worse arrhythmic outcome(9). Finally, EVM has been recently reported to be significantly more sensitive than contrast-enhancement-cardiac magnetic resonance in identify RV scar lesion (figure 13)(82). In accordance with the pathological findings concerning the progress of the fibrofatty dystrophy from the epicardium towards the endocardium; Garcia et al demonstrated that most patients with AC have a far more extensive substrate for VT using epicardium mapping than they do on RV endocardium(83). Due to the disappointing initial results endocardial ablation results(84), VT ablation as a line of therapy for patients with ARVC has been considered only in patients with end-stage ARVC, incessant VT, frequent implantable cardioverter defibrillator (ICD) interventions and intolerable antiarrhythmic drugs side-effects. However, more promising results have been recently published using more aggressive and sophisticated endocardial and epicardial substrate mapping and ablation techniques(83)(85). Yet, those results, being exclusive to very highly experienced centers, may be difficult to reflect in general practice.

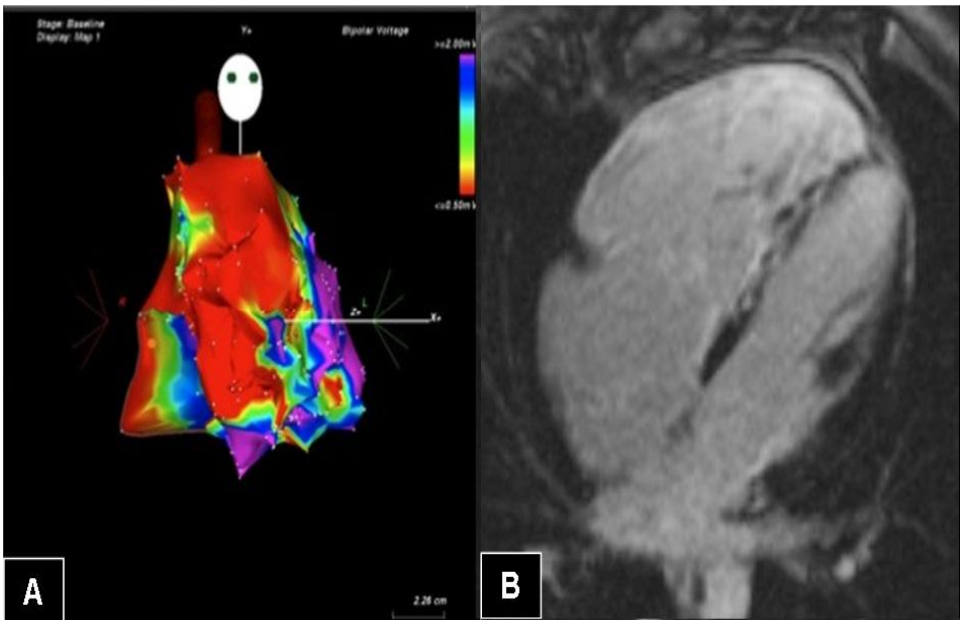


Figure 13. (A) Bipolar endomyocardial electrovoltage mapping of a patient with arrhythmogenic cardiomyopathy. Red color represents areas of a low voltage recordings <0.5 mV indicating a dense scar tissue. **(B)** Cardiac magnetic resonance of the same patient. Extensive fibrotic changes demonstrated by delayed gadolinium enhancement in most of the right ventricular free wall and extending into the interventricular septum (concordant to the electrovoltage mapping findings).

(Images courtesy of MP Marra, MD, University of Padua, Italy)

Pharmacological Therapy

Pharmacological treatment has been another challenging aspect in ARVC, given the small number of patient study populations and the near lack of randomized clinical trials. One of the largest series of pharmacologic therapy in AC is from Germany, first published in 1992 and updated in 2005 with 191 patients and 608 drug tests(86)(87). Sotalol at a dosage of 320-480 mg/d was the most effective drug resulting in a 68% overall efficacy. Combinations of amiodarone and beta-blockers were also efficacious.

Another large study was presented from the North American Registry in 2009(88). Of 108 patients in this registry, it was concluded that there was no clinically significant benefit in preventing malignant ventricular arrhythmias with beta-blockers. However there was a trend in the reduction in number of shocks in patients with implantable cardioverter defibrillator (ICD) and on a beta-blocker therapy. In opposition to the German registry, sotalol failed to show any clinical benefit, with worse outcomes associated with highest doses of sotalol. A small number (10 patients) were studied for amiodarone, and they showed 75% lower risk of any clinically relevant ventricular arrhythmias compared with all other patients. The mixed results from those two registries lead to the conclusion that there is not sufficient evidence to adequately guide physicians considering pharmacological management of ARVC(89).

Implantable Cardioverter Defibrillator

There is accumulating evidence that ICD provides life saving protection by effectively terminating ventricular arrhythmias in high risk patients with AC, coining ICD therapy as the gold standard line of management for those patients. One of the most seminal mutli-center studies of ICD therapy in ARVC is the DARVIN I study. The study was published in 2003, with a study population of 132 ARVC patients, 80% of them received ICD implant because of a history of either cardiac arrest or sustained VT (secondary prevention). Over the study period of 39 ±25 months, 3 deaths occurred (only one SCD; one for infective endocarditis and one for heart failure), 48% of patients (64 out of 132) had at least one appropriate ICD intervention. Fifty three of the 64 patients were receiving antiarrhythmic medication at the time of the first appropriate shock. Twelve percent of the patients received inappropriate ICD interventions and 16% had ICD-related complications (figure 14)(90). This was followed by the mutli-center DARVIN II study which focused on primary ICD prevention in high risk AC patients. The study included 106 patients with AC and no prior VF or VT who received an ICD because of one or more arrhythmic risk factors such as syncope, asymptomatic nonstained VT, familial SCD and inducibility of

sustained VT by programmed ventricular stimulation in the electrophysiological laboratory. During a mean follow up of 4.8 years, no death occurred, and 24% of the patients received appropriate ICD interventions and 19% received inappropriate interventions(91). In another large single center study, Witcher et al., reported 60 ARVC patients who received ICD therapy and were followed up for a period of 80±43 months. The majority of the cases received their ICD as a secondary prevention. With only 26% of event free follow up in the highest risk group, the study confirmed the improvement of long term prognosis of high risk AC patients who undergo ICD implantation(92).

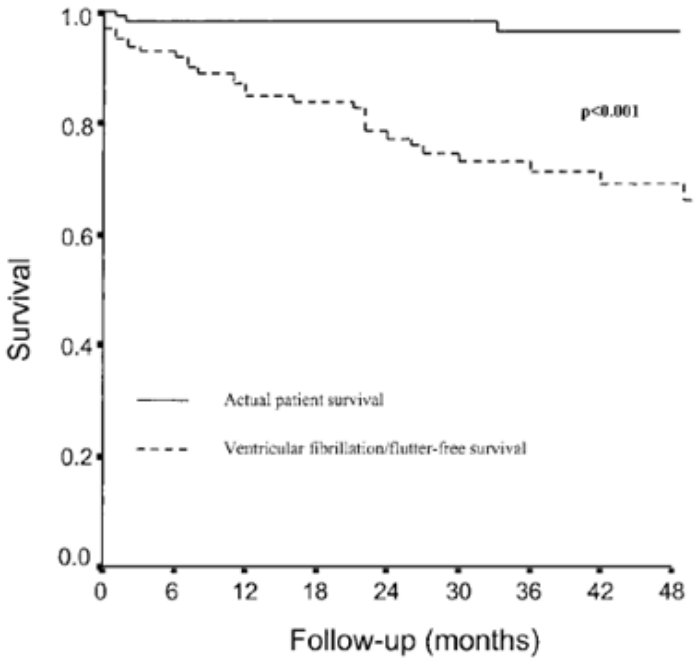


Figure 14. DARVIN I Kaplan-Meier analysis of actual patient survival (upper line) compared with survival free of ventricular fibrillation/flutter (lower line) that in all likelihood would have been fatal in the absence of the ICD. The divergence between the lines reflects the estimated mortality reduction by ICD therapy of 24% at 3 years of follow up.

Source: Corrado D, et al., 'Implantable Cardioverter-defibrillator Therapy for Prevention of Sudden Death in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy/dysplasia.', *Circulation*, 108 (2003), 3084–91.

Sports and Pre-participation Screening

The cornerstone in the management of ARVC as a cause of SCD relies on screening among high risk population. Corrado et al., have shown that the risk of sudden death from AC has been estimated to be 5.4 times greater during competitive sports than during sedentary activity (figure 15).(29) This can be attributable to the fact that physical exercise acutely increases the RV afterload and causes cavity enlargement, which in turn may elicit ventricular arrhythmias by stretching the diseased RV myocardium. This theory has been confirmed by Kirchof et al., in an experimental study on heterozygous plakoglobin-deficient mice, when compared with wild-type controls, the mutant mice had increased RV volumes, reduced RV function, and more frequent and severe VT of RV origin. Endurance training accelerated the development of RV dysfunction and arrhythmias in the plakoglobin-deficient mice(93). For more than 30 years a systemic pre-participation screening for athletes, based on 12-lead ECG, in addition to history and physical examination, has been in practice Italy. A time trend analysis of the incidence of SCD in athletes aged 12 to 35 years in the Veneto region in Italy between 1979 and 2004 has proved compelling evidence of the efficiency of this life saving screening strategy. The annual incidence of SCD in athletes decreased by 89% from 3.6 per 100,000 during the prescreening period to 0.4 per 100,000 in the late screening period (figure 16)(94). This is highly attributable to the efficiency of ECG in detecting HCM and AC as the most common causes of SCD amongst athletes. Moreover, during long term follow-up, no deaths were recorded in the disqualified athletes with HCM, suggesting that restriction from competition may reduce the risk of SCD(95).

Electrogenesis of T wave inversion

The T wave corresponds to repolarization of the ventricle and it is an electric manifestation of a normally asymmetrical repolarization process. An important electrocardiographic parameters obtained from body surface ECG, the Tpeak-to-end (Tp-e) interval and T wave inversion, have been shown to be a predictor of arrhythmias under a variety of clinical situations(96)(97)(98)(99). However, the electrogenesis of T wave and its pathological variants has been the subject of a long historical debate.

In 1883, Burdon-Sanderson and Page were the first to demonstrate that in the frog's heart, the wave of excitation spreads from the base to the apex of the ventricle(100). The record was diphasic, with the first positive (R) wave followed by a negative (T) wave. They also demonstrated that the T wave corresponds to repolarization of the ventricle. Similar series of experiments by Bayliss and Starling in 1892 in the canine heart showed that the T waves are usually upright in mammals(101). This was followed by Mines on frog's heart using Einthoven's String Galvanometer in 1913(102).

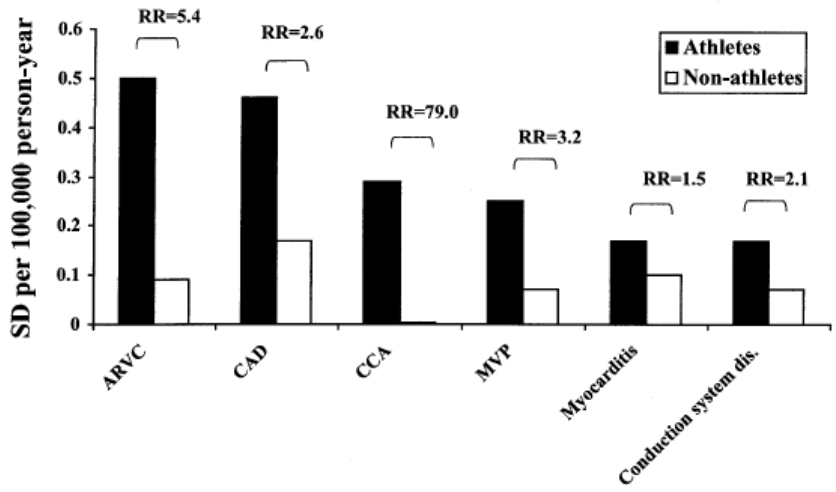


Figure 15. Incidence and relative risk (RR) of sudden death (SD) for specific cardiovascular causes among athletes and non-athletes. ARVC: arrhythmogenic right ventricular cardiomyopathy; CAD: coronary artery disease; CCA: congenital coronary artery anomaly; MVP: mitral valve prolapse.

Source: Corrado D, et al., 'Does Sports Activity Enhance the Risk of Sudden Death in Adolescents and Young Adults?', *Journal of the American College of Cardiology*, 42 (2003), 1959–63.

Mines stated that the T wave is an electric expression of asymmetrical passing off of excitation (repolarization) in different parts of the ventricles and that the polarity of the T wave can be predicted by changing the duration of the action potential in a controlled manner. In 1931, Wilson et al. put forward the hypothesis that the concordance of the T wave with the R wave on the surface ECG can be explained by assuming that the depolarization and the repolarization waves must travel in opposite directions at least in some parts of the ventricle(103). The biophysical principle behind this hypothesis requires that the cells that activate first have to repolarize last to produce a T wave of the same polarity of that of the R wave. In other words, the action potential duration (APD) in the cells that are excited first should be significantly longer than the cells that are excited last.

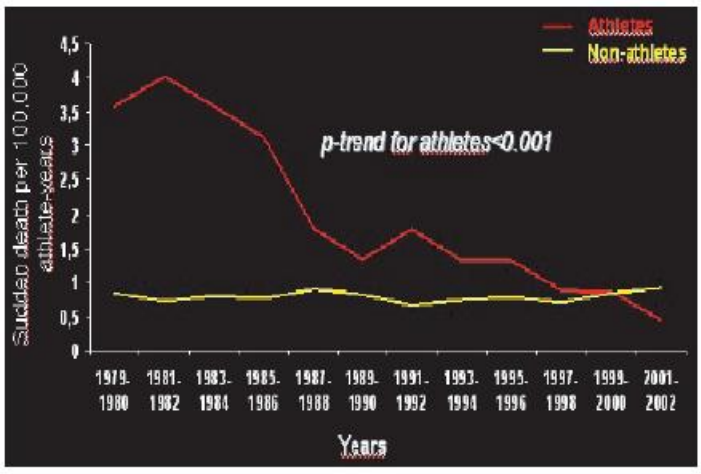


Figure 16. Annual incidence rates of SCD per 100,000 person-years among screened competitive athletes and unscreened nonathletes aged 12 to 35 in Veneto region, Italy. Note the sharp decline of the screened athlete graph.

Source: Corrado D, et al., 'Trends in Sudden Cardiovascular Death in Young Competitive Athletes After Implementation of a Preparticipation Screening Program.', *JAMA : the journal of the American Medical Association*, 296 (2006), 1593–601.

In an attempt to explain the positive polarity of the T wave in mammals, Noble and coworkers in 1976 recorded action potentials from tissue slices dissected from the "base" and the "apex" of the sheep ventricle and showed that at steady state, APD is longer at the "base" as compared with the "apex".

They concluded that such a difference could account for a positive polarity of the T wave in mammals(104). This series of experiments laid down the foundation of the controversial hypothesis that apico-basal difference in the time course of repolarization underlies the genesis of a positive T wave. The theory of apico-basal dispersion of repolarization as a basis of the electrocardiographic T wave dominated the medical literatures until the 1990s when the discovery of M cells, and the development of the left ventricular wedge technique suggested that the transmural dispersion of repolarization may contribute importantly to the genesis of the T wave(105)(106)(107)(108)(109). An increasing number of studies have shown that the ventricular myocardium is not a homogeneous structure, but it is comprised of 3 distinct cell types, i.e., epicardial, subendocardial and endocardial cells, with clearly distinct electrophysiological and pharmacological properties. The M cells are located in deep subendocardium of the canine LV(105)(106). The hallmark of M cells is the ability of its action potential to prolong more than that of the epicardium or endocardium in response to slowing of the rate or in response to agents that prolong APD. The development of the canine and rabbit left ventricular wedge models have provided the ability to record transmembrane action potentials from 3 different myocardial cell types simultaneously (figure 17). The presence of an important transmural repolarization gradient in ventricle has been well established in a variety of species. This model coupled with mathematical simulations of the myocardium

provide evidence in support of a predominant role for the transmural voltage gradient in the genesis of the T wave(110)(111).

Despite the remarkable ability of wedge preparation to reproduce the electrocardiographic and arrhythmic manifestations of a wide variety of syndromes observed in clinical practice, it has its limitations. Some argue that the canine left ventricular wedge is too small a sample and does not reflect what might happen in an intact heart(112). In fact, refuters of the transmural gradient theory point to that only in one study study of El-Sherif et al, a small prolongation of activation-recovery intervals in midmural regions was found in young dogs, albeit only at long cycle lengths(113). In the human heart, several series could not find a transmural gradients in activation-recovery interval or repolarization times (114)(115). Furthermore, an analysis of the data from the study on monophasic action potential mapping in humans by Franz et al showed that epicardial repolarization occurred later than endocardial repolarization (116)(117). In addition, in the study of Chauhan et al, repolarization time in the anteroseptal right ventricular endocardium in cardiomyopathy patients without arrhythmias was on average 288 ms, and left ventricular epicardial repolarization time adjacent to the septum was 287 ms, demonstrating no significant gradient between the endocardium and epicardium (118). Although the exact mechanism for the genesis of T wave abnormalities on the surface ECG remains a matter of scientific controversy, their clinical utility as an index of arrhythmogenesis and prognostic outcome in cardiomyopathies is gaining increasing recognition(119).

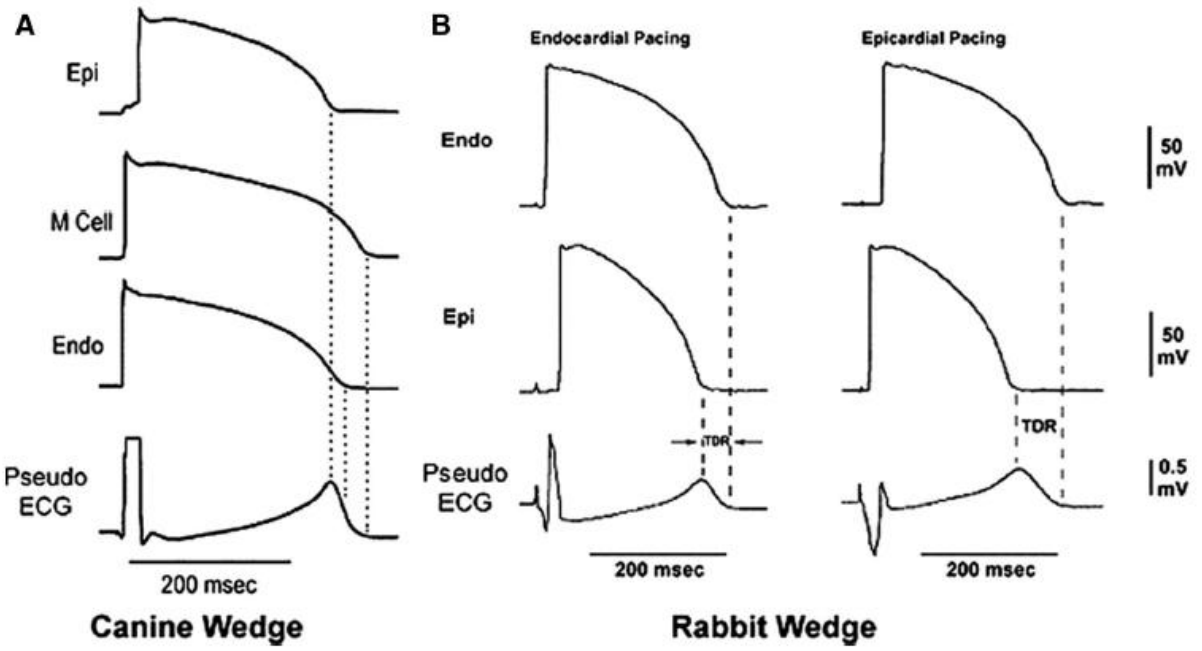


Figure 17. (A) The cellular basis of the T wave in the canine left ventricular wedge preparation. Simultaneous recordings of action potential with of 3 different cell type with a pseudo-ECG are shown. Note that the opposing voltage gradient on either side of the M region leads to inscription of the T wave. The peak of the T wave coincides with the end of repolarization of the epicardial cell and the end of the T wave coincides with the end of repolarization of the M cells. **(B)** The cellular basis of the T wave in the rabbit left ventricular wedge. In the rabbit, the entire endocardium has the same electrophysiological properties as M cells. Therefore, the end of the T wave coincides with the end of repolarization of the endocardium in the rabbit. Epicardial pacing leads to earlier activation of epicardial cells with shorter APD and delays the activation of endocardial cells with a longer APD, leading to an increase in QT and Tp-e interval. Epi Epicardium; Endo, Endocardium; AP, action potential.

Source: Yan G and Antzelevitch C, 'Cellular Basis for the Normal T Wave and the Electrocardiographic Manifestations of the long-QT Syndrome.', *Circulation*, 98 (1998), 1928–36.

AIM OF THE WORK

To assess the prognostic value of the presence and extent of electroanatomical scar detected by endocardial voltage mapping in patients with arrhythmogenic right ventricular cardiomyopathy and to evaluate the non invasive predictors of the electroanatomical scar size.

To study the exercise-induced right precordial negative T wave changes in patients with arrhythmogenic right ventricular cardiomyopathy

METHODS AND RESULTS

Non-invasive predictors of electroanatomic scar size in arrhythmogenic right ventricular cardiomyopathy

Methods

Study Population

The study population included 69 consecutive patients (47 males; median age 35 years [28–45]) with ARVC/D who were referred at the Division of Cardiology of the University of Padova, Italy for risk stratification. All patients underwent detailed cardiac evaluation including family history, physical examination, 12-lead ECG recording, signal-averaged ECG; 24-hour Holter monitoring, exercise stress testing, echocardiography and cardiac catheterization including RV and left ventricular (LV) angiography in the right and left anterior oblique view, and coronary angiography.

All patients met the International Task Force (ITF) criteria (2 major criteria or 1 major criterion plus 2 major criteria or 4 minor criteria) for diagnosis of definite ARVC Diagnosis was established according to the original ITF criteria(62) and confirmed using the recently revised criteria(11). All patients underwent intracardiac electrophysiological study with PVS for assessing VT/VF inducibility and high density EVM for imaging and quantification of abnormal RV EVM. A subanalysis focused on the group of patients who had showed an abnormal EVM with evidence of ≥1 RV-EAS to assess the noninvasive features that correlate best with the presence and the extent of the EAS. The study was approved by the institutional review board, and all patients gave their informed consent.

Echocardiogram

Echocardiograms were obtained using a 2.5- to 4-MHz transducer (Hewlett Packard model 5500, Andover, Massachusetts) and included M-mode, 2-dimensional, and Doppler examinations. Parasternal, apical and subcostals views were performed to evaluate the presence of right-ventricular wall motion abnormalities. Right ventricular end-diastolic volumes (RV-EDV) was calculated using an area-length method derived from orthogonal planes (apical 2-chamber and short-axis subcostal views). Right ventricular fractional area change (RV-FAC) was derived from the calculated systolic and diastolic RV areas on apical 4-chamber view. Left ventricular (LV) end-diastolic volume, end-systolic volume and ejection fraction were calculated using the Simpson's method.

12-lead ECG and SAECG

ECGs were evaluated on standard speed paper. The following ECG abnormalities were analyzed:

- low QRS voltage in limb leads (≤0.5 mV)
- QRS duration ≥110 msec in V1-V3
- delayed S-wave upstroke in leads V1 to V3 (> 60 msec from nadir of S wave to baseline) in the absence of complete right-bundle branch block
- epsilon waves (defined as reproducible low amplitude signals between end of QRS complex to onset of the T-wave in the right precordial leads V1-V3
- left axis deviation (< -30°)
- right axis deviation (> 90°)
- T-wave inversion ≥1 mm in depth in ≥2 adjacent leads.

Three patients had complete right bundle branch block and were excluded from analysis of repolarization abnormalities.

SAECGs were obtained using a MAC15 system (Marquette Inc., Milwaukee, Illinois). The following parameters were evaluated for each filter (25 and 40 Hz):

- filtered QRS duration (fQRSD)
- duration of the low-amplitude signals (<40 mV) in the terminal portion (LAS-40)
- root mean square voltage of the last 40 ms (RMS-40).

According to the 2010 Revised International Task Force Criteria for ARVC, ventricular late potentials were considered present when 1 or more of the following criteria were fulfilled: 1) fQRSd ≥114 ms; 2) LAS-40 ≥38 ms; 3) RMS-40 ≤20 uV (11).

Electrophysiological Study

All antiarrhythmic drugs were discontinued 5 half-lives (6 weeks for amiodarone) before the electrophysiological study. Programmed ventricular stimulation protocol included 3 drive cycle lengths (600, 500, and 400 ms) and 3 ventricular extrastimuli while pacing from 2 RV sites (apex and outflow tract). Programmed ventricular stimulation was considered positive if either a VF or sustained VT (i.e., one that lasted ≥30 seconds or required termination because of hemodynamic compromise) was induced. Programmed ventricular stimulation was repeated after intravenous isoproterenol infusion in those patients with effort induced non sustained VT (16 of 53, 26%).

Electroanatomic Voltage Mapping

At the time of electrophysiological study, all patients underwent detailed EVM by the CARTO system (Biosense-Webster) during sinus rhythm. A 7-F Navi-Star (Biosense- Webster) catheter, with a 4-mm distal tip electrode and a 2-mm ring electrode with an interelectrode distance of 1 mm, was introduced

into the RV under fluoroscopic guidance and used as the mapping/ ablation catheter. The catheter was placed at multiple sites on the endocardial surface of RV free wall (infero-basal, antero-lateral free wall, apex, and RV outflow tract) and septum to reconstructed the 3-dimensional geometry of the RV chamber. Bipolar electrogram signals (filtered at 10–400 Hz and displayed at 100 mm/s speeds on the CARTO system) and unipolar signals (filtered at 1–240 Hz and displayed at 100 mm/s speeds on the CARTO system) were recorded and analyzed simultaneously with regard to amplitude, duration, relation to the surface QRS, and presence of multiple components. Duration of an endocardial bipolar electrogram was measured as the time from the earliest electric activity to the artifact produced by the decay of the amplified filtered signal. Bipolar signals were recorded between the distal electrode pair, unipolar signals between the distal tip of the ablation catheter (cathode) and the Wilson central terminal. In our study the following tools were used to avoid false low voltage recordings:

adequate catheter contact was confirmed by concordant catheter tip motion with the cardiac silhouettes on fluoroscopy

a recording was accepted and integrated into the map when the variability in cycle length, local activation time stability, and maximum beat-to-beat difference of the location of the catheter (automatically detected by the CARTO system) were <2%, <3 ms, and <4 mm, respectively (these parameters, combined with the stability of the impedance reading, were used to exclude low amplitude signals attributable to poor endocardial catheter contact)

in the presence of a low voltage area, ≥3 additional points were acquired in the same area to confirm the reproducibility of the voltage measurement.

Particular attention was paid to validate the acquisition of endocardial points from the RV infero-basal region, because of the recognized risk of poor tissue contact in this area. Because of the potential high mapping error and to avoid overestimation of low voltage RV areas resulting from inclusion of normal annular fibrous tissue, the immediate perivalvular areas (ie, within 1.5 cm of the valvular locations on postprocessing measurement) were excluded in the analysis of endocardial low voltages.

Values of normal RV endocardial voltages were established by RV EVM in 6 reference patients without structural heart disease, who underwent electrophysiological study for evaluation of supraventricular tachycardia. RV septal endocardial sites (23±5) were excluded and only RV free-wall electrogram recordings (207±16 points sampled), either bipolar or unipolar, were analyzed. Normal bipolar electrograms were sharp with ≤3 rapid deflections; the mean electrogram duration was 34.8±1.2 ms and the mean amplitude 5.3±0.9 mV, with 95% of all electrogram signals <66 ms and >1.47 mV. In addition, we analyzed the amplitude of unipolar electrograms, which was 10.3±0.6 mV with 95% of all unipolar signals recorded having an amplitude >5.96 mV. Then in the present study the reference values used to define normal RV electrogram amplitude was set at 1.5 mV for bipolar signals and 6.0 mV for unipolar signals, which were the values above which 95% of all bipolar and unipolar electrogram voltages from the endocardium of normal RVs were included.

We considered normal bipolar electrocardiograms those with sharp and ≤3 spikes, amplitude >1.5 mV, and duration ≤70 ms. We defined as fragmented electrograms those characterized by multiple deflections (>3), amplitude ≤1.5 mV, and duration >70 ms. Normal amplitude electrograms (bipolar >1.5 mV and unipolar >6.0 mV) were represented in the electroanatomic CARTO map by the color purple, whereas low-amplitude signals were represented by non-purple range of colors. Color red indicated dense scar, which was arbitrarily defined as bipolar signal amplitude <0.5 mV and unipolar signal amplitude <3.5 mV, according to previously reported criteria. 20–24 An EVM was considered abnormal in the presence of a single or multiple RV low voltage areas ≥1 cm2 including ≥3 adjacent points with a bipolar signal amplitude <1.5 mV and an unipolar signal amplitude <6.0 mV.

Complete endocardial maps were obtained in all patients to ensure reconstruction of a 3-dimensional geometry of the RV chamber and to identify areas of abnormal electrograms in the RV free wall. The

septum was excluded from the analysis. Regions showing low-amplitude signals were mapped with greater point density to delineate the extent and borders of endocardium electroanatomic scar areas. The extent of low-voltage areas was estimated by using a CARTO incorporated area calculation software

(CARTO, Biosense Webster Inc. Diamond Bar, CA) and was expressed both as total RV area and percentage of RV area, excluding tricuspid and pulmonary valvular annuli.

Follow-Up

The follow-up data were obtained prospectively during regular outpatient visits at 6- to 12-month intervals. Routine ICD interrogation and ECG recordings at the time of symptoms were used to document the occurrence of spontaneous VT during follow-up. The study outcome was the index combined end point of major arrhythmic events such as sudden death (SD), cardiac arrest attributable to VF, sustained VT, or appropriate ICD intervention. Sudden death was defined as any natural death occurring instantaneously or within one hour from symptoms onset. Sustained VT was defined as tachycardia originating in the ventricle with rate >100 beats/min and lasting >30 seconds or requiring an intervention for termination. Appropriate ICD intervention was defined as a device shock or antitachycardia overdrive pacing delivered in response to a ventricular tachyarrhythmia and documented by stored intracardiac ECG data. Ventricular fibrillation and VT were defined as a ventricular tachyarrhythmia with a cycle length ≤240 ms or >240 ms respectively. Implantable cardioverter defibrillator were routinely programmed to include a monitoring zone that identified VT with a rate >160 bpm.

Statistical Analysis

Results are summarized as mean±standard deviation (SD) or median with 25 to 75 percentiles for normally distributed and skewed variables, respectively. Normal distribution was assessed using Shapiro–Wilk test. Categorical differences between groups were evaluated by the $\chi 2$ test of the Fisher exact test as appropriate. Paired and unpaired t tests were used to compare normally distributed continuous variables respectively obtained from the same patient and different patients; paired and unpaired Rank Sum test were used for skewed continuous variables. Kaplan–Meier analysis was used to estimate the survival

distributions of the index combined end point and to show the difference in survival between patients with normal versus abnormal bipolar EVM and positive versus negative PVS. Start of follow-up was defined as the date of the initial EVM. Patients were censored at the time of their first event or the time of their last clinical follow-up. The mean event rate per year was evaluated by the number of events occurring during the follow-up divided by the number of patients multiplied by the average duration of follow-up. The independent correlation of traditional clinical predictors of arrhythmic risk in ARVC/D with the index combined end point during follow-up was determined by means of univariate and multivariable Cox regression analysis. Variables with a probability value <0.15 were integrated into multivariable analysis using Cox proportional-hazard models to estimate the Hazard ratio (HR) and to identify independent predictors of major arrhythmic events. The Cox model was used to calculate

the relation between amount of RV low-voltage areas and hazard ratios. HRs and confidence intervals (CI) are presented both in univariate and multivariable analysis. The c-statistic method was used to estimate the best cut-off value of bipolar low-voltage area to discriminate between patients with and those without major arrhythmic events during follow-up.

For the sub-analysis of EAS-positive patients, the Spearman's correlation coefficient (rho) was used for correlating RV-EDV and RV-FAC with the EAS area. The Spearman coefficient ranges from ±1 (perfect correlation) to 0 (no correlation). The Kruskal Wallis test was used for testing the association between the extent of negative T-waves across the 12 leads and RV-EAS% area. Variables associated with the EAS area at univariate analysis with a p value < 0.1 were integrated into a multivariate linear regression model. The regression coefficient B is defined as the expected change in the dependent variable (RV-EAS% area) for a one-unit change in the independent variable. Event-free survival curves were drawn with the Kaplan-Meier method and compared by the logrank test. A value of P<0.05 was considered significant. Statistics were analyzed with SPSS version 17 (SPSS Inc, Chicago, IL).

Results

Clinical Characteristics

Baseline clinical characteristics and instrumental findings are summarized in Table 3. The study population included 69 consecutive patients (47 men; median age, 35 years [28–45]).

Twenty-eight patients (40%) had a family history of ARVC (n=12, 17%) or premature (<35 years) sudden death (n=16, 23%). Twenty-two (32%) patients had a history of cardiac arrest or syncope. Ventricular tachycardias were documented in 53 (76%) patients and included sustained VT (n=9, 13%) or nonsustained VT (n=44, 63%). There were 15 morphologies of sustained VT, all with a left bundle branch pattern, with a superior axis in 8, inferior axis in 4, and undetermined axis in 3. Right ventricular dilatation/dysfunction was observed at echocardiography/angiography in all patients. Multiregional

wall motion abnormalities (akinesia, diskinesia or bulging involving ≥2 RV regions) were found in 25 (36%) patients. Thirty-four (49%) patients were inducible at programmed ventricular stimulation to either sustained monomorphic VT (n=23) or VF (n=11). Among 8 noninducible patients, 2 experienced exercise induced arrhythmic events during follow-up. At enrolment, 57 (82%) patients with VT or frequent premature ventricular beats were empirically treated with antiarrhythmic drug therapy, which consisted of sotalol (n=22), amiodarone either alone (n=9) or in combination with beta blockers (n=14), beta blockers (n=7), and flecainide (n=5).

Table 3.Clinical characteristics of overall sample and according to results of bipolar-EVM.

	Overall sample N = 69	Abnormal bipolar-EVM N = 53 (77%)	Normal bipolar-EVM N = 16 (23%)	P
Age (yrs), (mean ± SD)	37.3±13.6	37.4±12.8	37.3±16.4	0.42
Sex (male), n (%)	47 (68)	36 (68)	11 (69)	1.00
Family history of sudden death (<35 years), n (%)	16 (23)	15 (28)	1(6)	0.12
Family history of ARVC/D, n (%)	12 (17)	11 (20)	1(6)	0.34
History of cardiac arrest or syncope, n (%)	22 (32)	20 (37)	2 (12)	0.07
Right precordial T-wave inversion (V1-V3), n (%)	49 (71)	41 (77)	8 (50)	0.04
Positive SAECG, n (%)	34 (49)	29 (54)	5 (31)	0.13
Premature Ventricular Beats > 1000/24 hours	59 (85)	45 (85)	15 (94)	0.72
Non-sustained VT, n (%)	44 (63)	33 (62)	11 (69)	0.81
Sustained VT, n (%)	9 (13)	8 (15)	1 (6)	0.72
RVEDV (ml/m2, mean ± SD)	85±31	87±34	76±18	0.09
RVFAC (%, mean ± SD)	36±6	36±6	37±7	0.82
LVEDV (ml/m2, mean ± SD)	67±17	67±15	67±22	0.94
LVEF (%, mean ± SD)	57±10	56±10	58±6	0.26
Multiregional RV-WMA*, n (%)	25 (36)	22 (41)	3 (19)	0.01
Inducibility at PVS, n (%)	34 (49)	26 (49)	8 (50)	1.00
- VT, n (%)	28 (41)	22 (42)	6 (38)	0.93
- VF, n (%)	6 (9)	4 (8)	2 (13)	0.91
ICD implantation, n (%)	31 (44)	29 (54)	2 (12)	0.004

* multiregional WMA=akinesia, diskinesia or bulging in ≥2 RV regions

ARVC/D=arrhythmogenic right ventricular cardiomyopathy/dysplasia; EDV=end diastolic volume; EF=ejection fraction; FAC=fractional area change; LV=left ventricle; PVS=programmed ventricular stimulation; RV=right ventricle; SAECG=signal averaged electrocardiogram; SD=standard deviation; VT=ventricular tachycardia; WMA=wall motion abnormalities.

Electroanatomic Voltage Mapping

Endocardial voltage mapping was successfully acquired during sinus rhythm in all patients, with a mean number of sites sampled of 195±22.

Bipolar EVM

An abnormal bipolar RV EVM was recorded in 53 (77%) patients. Patients with and without evidence of abnormal bipolar EVM had similar baseline clinical characteristics, except for multiregional RV wall motion abnormalities, which was significantly more prevalent in the abnormal bipolar EVM group. In patients with an abnormal bipolar EVM the median RV low-voltage area was 39.1 cm2 (13.2–67.8) with a median percent RV area of 24.8% (7.2–31.5; Figure 18). The involved RV regions were infero-basal in 49 (71%) patients, antero-lateral in 28 (40%), RV outflow tract in 25 (36%), and apex in 15 (22%) (Figure 19).

Mean bipolar amplitude of local electrograms recorded from within RV electroanatomic scar areas was significantly lower than that sampled from unaffected RV areas (0.38±0.11 vs. 5.2±0.6mV; P<0.001). Similarly, bipolar electrograms from low-voltage areas had a longer mean duration (78.9±18 vs. 33.5±7.8ms; P<0.001) and more often extended beyond the offset of the surface QRS (64% vs. 7%; P<0.001), compared with electrograms sampled from regions with preserved electrogram voltage (Figure 20). Fragmented bipolar electrograms (i.e., signals with > 3 deflections, amplitude ≤1.5 mV, and duration >70 ms) were recorded in 47 of 53 (88%) patients with an abnormal bipolar EVM. In 16 patients (23%), EVM was normal, with preserved bipolar endocardial electrogram amplitude (4.8±1.3 mV) and duration (35.3±0.8 ms).

Unipolar EVM

In the 53 patients (77%) with abnormal bipolar EVM, unipolar EVM recorded significantly more extensive RV electroanatomic scar involvement with a median RV low-voltage area of 68.5 cm2 (22.9–98.7) and median percent RV area of 64.8% (39.8–95.3) compared with low voltages obtained by bipolar EVM (P<0.009; Figure 18). In all 16 patients (23%) with normal bipolar EVM, the use of unipolar EVM technique unmasked ≥1 regions of low voltage unipolar electrogram abnormality 37.3 cm2 (12.1–48.9); 26.2% (11.6–38.2; Figure 18).

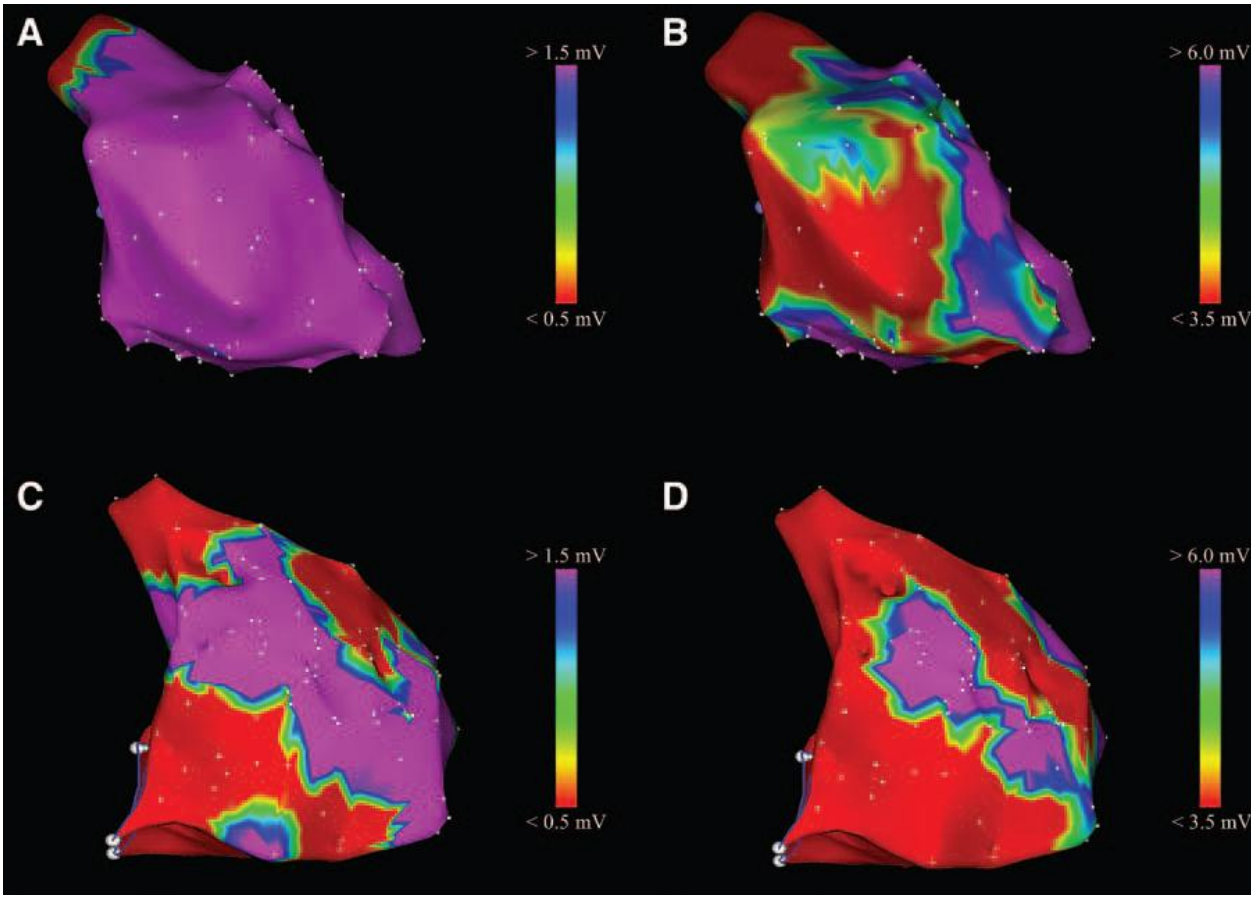


Figure 18. Representative bipolar and unipolar right ventricular (RV) endocardial voltage mapping (EVM) from 2 arrhythmogenic right ventricular cardiomyopathy (ARVC) patients. Patient #16: Right anterior oblique view of RV bipolar EVM showing preserved bipolar voltages values **(A)**; right anterior oblique view of RV unipolar EVM from the same patient unmasking the presence of a significant

electroanatomic scar **(B)**. Patient #47: Compared with right anterior oblique view of bipolar RV EVM **(C)**, unipolar RV EVM **(D)** reveals a greater burden of low voltage electrogram area involving the RV outflow tract, infero-basal, and apex regions.

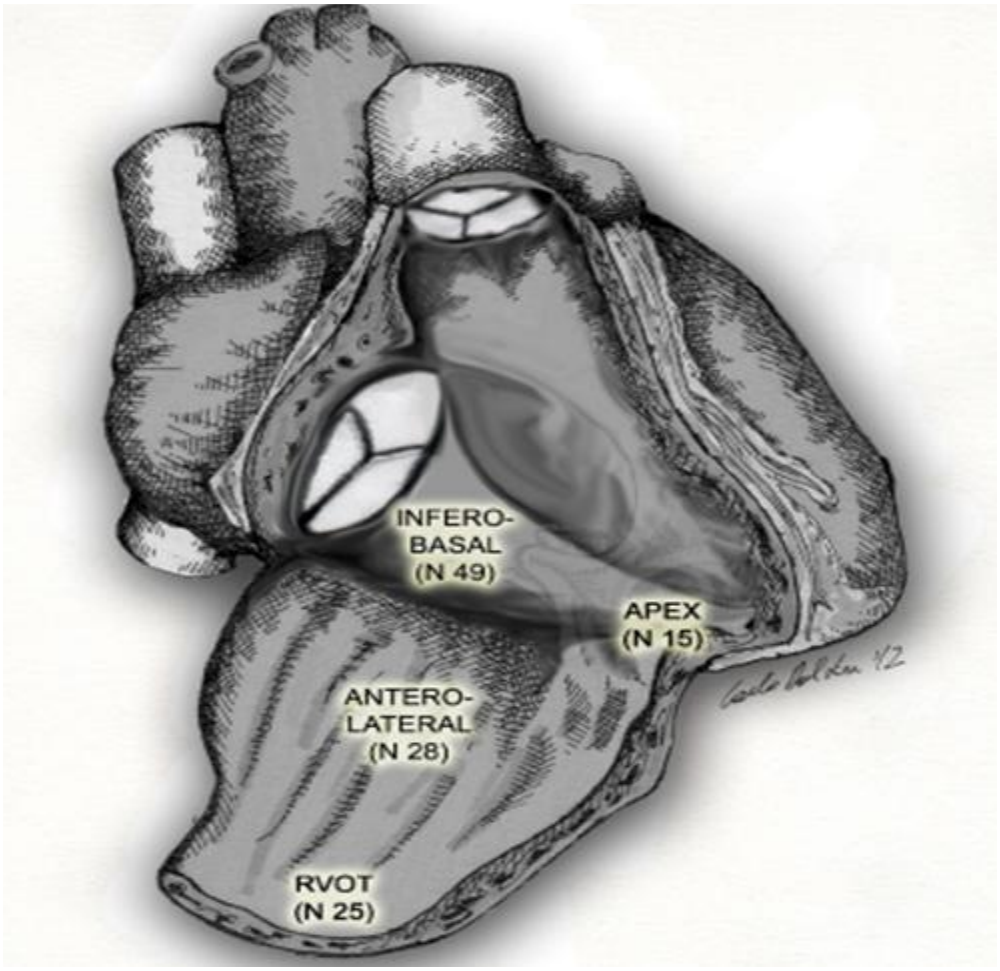


Figure 19. Anatomic representation of regional distribution of bipolar low-voltage areas in the RV free-wall. The septum was excluded from the analysis. RVOT = right ventricular outflow tract.

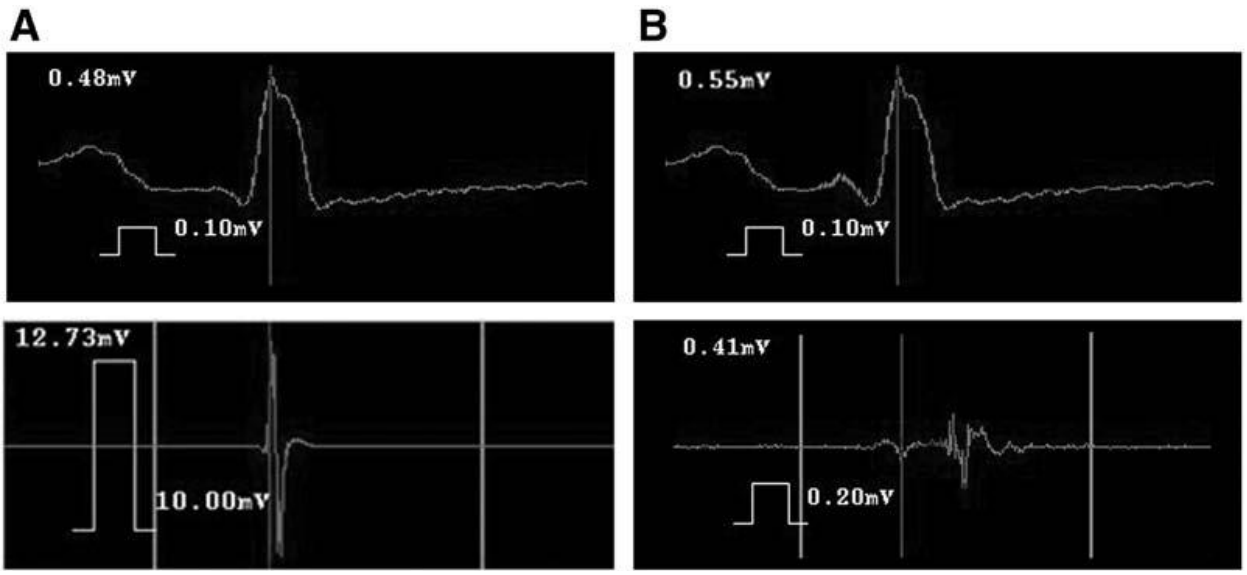


Figure 20. Surface ECG (top) and bipolar intracardiac electrocardiograms (bottom) sampled from within normal **(A)** and low-amplitude **(B)** right ventricular (RV) area in the same arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC) patient. Normal voltage electrogram is characterized by a sharp, biphasic deflection with large amplitude and short duration (A). By comparison, electrogram recorded from low-voltage areas (i.e., electroanatomic scar) are fragmented with late activation and prolonged duration beyond the QRS complex.

Follow-Up

During a median follow-up of 41 (28–56) months, 19 patients (27.5%) reached the composite arrhythmic end point, with a 6.7% annual rate of major arrhythmic events. Eleven patients (16%) had an episode of sustained VT, 7 (10%) experienced ≥1 appropriate ICD interventions, either against VF (n=4) or VT (n=3), and 1 (1.4%) died suddenly. Among the 4 patients who experienced VF, 1 underwent orthotopic heart transplantation because of intractable recurrent VF storms. Table 4 shows the clinical characteristics of patients with or without major arrhythmic events during follow-up. Patients who

experienced arrhythmic events significantly more often had a history of cardiac arrest or syncope (73% vs. 16%; P=0.001), and abnormal bipolar EVM (100% vs. 68%; P=0.003).

Figure 21 shows Kaplan–Meier analysis of survival from the index combined end point of sustained VT, appropriate ICD intervention, and SCD for the overall population, stratified by bipolar EVM findings. Overall, the annual event rate was 11.4%/y in patients with an abnormal bipolar EVM and 0%/y with a normal bipolar EVM (logrank: P=0.02).

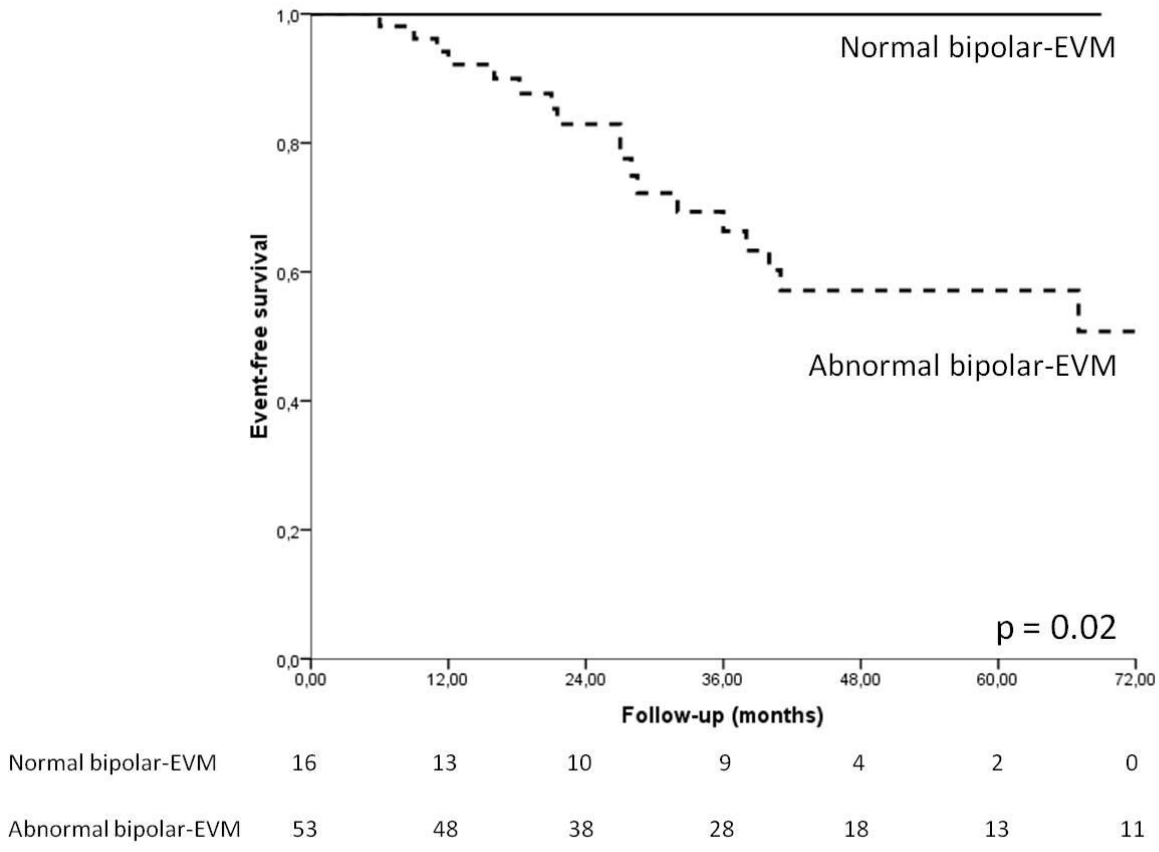


Figure 21. Kaplan–Meier analysis of freedom from adverse events stratified by the presence of abnormal bipolar endocardial voltage mapping (EVM).

Table 4. Characteristics of patients with and without arrhythmic events during follow-up.

	Events N=19 (28%)	No events N=50 (72%)	P
Age (yrs), (mean ± SD)	34.7±13.1	38.3±13.6	0.33
Sex (male), n (%)	14 (74)	36 (72)	0.95
Family history of sudden death (<35 years), n (%)	6 (32)	10 (20%)	0.39
History of cardiac arrest or syncope, n (%)	14 (73)	8 (16)	0.001
Non-sustained VT, n (%)	10 (53)	34 (68)	0.42
Sustained VT, n (%)	6 (32)	6 (12)	0.06
RVEVD (ml/m2, mean ±S D)	85.3±28.6	84.4±32.0	0.91
RVFAC (%, mean ± SD)	37.3±5.9	37.2±6.6	0.82
LVEVD (ml/m2, mean ± SD)	62.0±12.4	68.9±17.8	0.11
LVEF (%, mean ± SD)	50.4±7.9	50.2±9.0	0.93
Fragmented bipolar electrograms	15 (79)	32 (64)	0.37
Inducibility at PVS, n (%)	11 (58)	23 (46)	0.46
VT, n (%)	9 (47)	19 (38)	0.67
VF, n (%)	2 (11)	4 (8)	1.00
Antiarrhythmic drug therapy, n (%)	15 (79)	42 (84)	0.96
Abnormal bipolar-EVM, n (%)	19 (100)	34 (68)	0.003
Abnormal unipolar-EVM, n (%)	19 (100)	50 (100)	1.00

Abbreviations as in Table 3.

Electrophysiological Study

Overall, the annual event rate was 6.1%/y in patients who were inducible at PVS and 7.1%/y in those who were non-inducible (logrank: P=0.46; Figure 22). Of 34 patients who were inducible at PVS, 23 (68%) did not experience major arrhythmic events during the follow-up (i.e., false positives), whereas 8 of 35 (23%) non-inducible patients had malignant events (i.e., false negatives). The type of ventricular tachyarrhythmia which was inducible at the time of PVS (either VT or VF) did not predict either the presence of bipolar electroanatomic scar or the occurrence of arrhythmic events during follow-up. Patients with and without events during follow-up had a similar prevalence of RV fragmented bipolar electrograms (79% vs 64%).

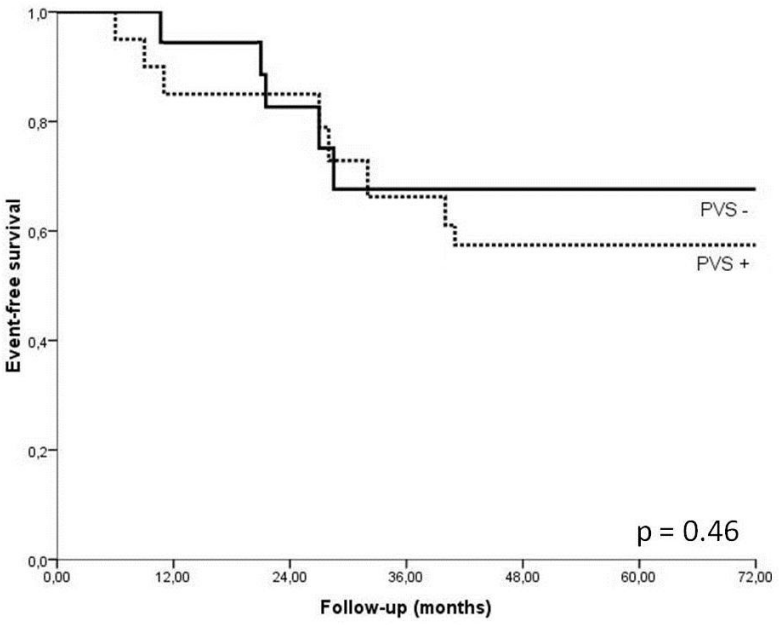


Figure 22. Kaplan–Meier analysis of freedom from adverse events stratified by inducibility of ventricular arrhythmias by programmed ventricular stimulation (PVS) ; (PVS +: inducible); (PVS-: non inducible).

Predictors of Events

Predictors of adverse events during follow-up are listed in Table 5.

Table 5. Predictors of arrhythmic events during follow-up

	Univariate analysis			Multivariable analysis		
	HR	CI	P	HR	CI	P
Age	1.0	1.0-1.0	0.7			
Sex (male)	1.1	0.4-3.3	0.8			
Family history of sudden death	1.1	0.4-3.0	0.9			
History of cardiac arrest or syncope	3.4	1.4-8.8	0.03	2.4	0.8-6,2	0.11
Non-sustained VT	1.8	0.3-5.7	0.7			
Sustained VT	1.1	0.4-2.5	0.9			
RVEVD (ml/m2)	1.1	0.9-1.3	0.8			
RVFAC (%)	1.0	0.9-1.1	0.5			
LVEVD (ml/m2)	0.9	0.9-1.0	1			
LVEF (%)	1.0	0.9-1.1	0.9			
Fragmented bipolar electrograms	1.2	0.7-3.1	0.32			
Inducibility at PVS	1.4	0.5-5.0	0.4			
Antiarrhythmic drug therapy	0.9	0.3-3.4	0.8			
Abnormal bipolar-EVM†	1.7	1.5-2.0	<0.001	1.6	1.2-1.9	<0.001
Abnormal unipolar-EVM†	1.3	0.6-4.3	0.3			

† *HR for 5% interval* Abbreviations as in Table 3.

Univariate predictors of events were a previous history of cardiac arrest or syncope and extent of abnormal bipolar EVM. The overall arrhythmic risk increased with percentage of abnormal bipolar EVM (HR, 1.7 per 5% abnormal EVM increase; 95% CI, 1.5–2.0; P<0.001; Figure 23). At multivariable analysis the amount of abnormal bipolar EVM was an independent predictor of events (HR, 1.6 per 5% increase of abnormal EVM percentage; 95% CI, 1.2–1.9; P<0.001). The amount of abnormal bipolar EVM was a predictor of events (HR, 1.4 per 5% increase of abnormal bipolar EVM percentage; 95% CI, 1.1– 1.9; P=0.004) even in the subgroup of 55 patients without previous sustained VT or previous cardiac arrest. According to c-statistic, the best cut-off value for abnormal bipolar EVM % area was 27.8% (c=0.74).

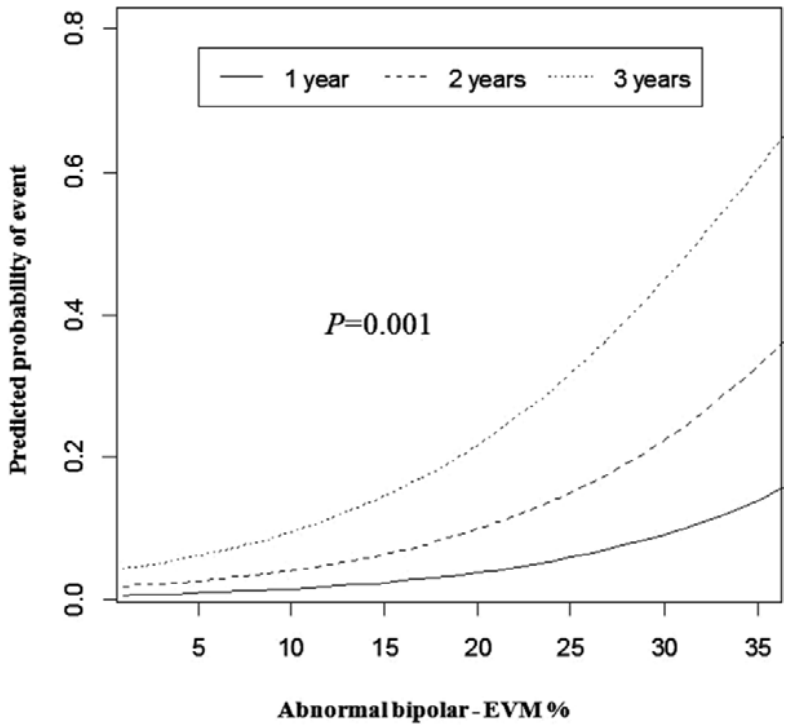


Figure 23. Predicted probability of reaching the combined arrhythmic end point at 1, 2, and 3 years on the basis of the extent of abnormal bipolar endocardial voltage mapping (EVM).

Subanalysis of the EAS positive group

Clinical Characteristics

Data from forty nine out of the 53 patients [38 males, median age 35 (28-46) years] who showed an abnormal EVM with evidence of ≥1 RV-EAS were used for further correlation of non invasive features with the extent of EAS (figure 24). The remaining four patients were excluded from the subanalysis for the poor quality of their non-invasive data. The baseline clinical characteristics and instrumental findings of the study sample are summarized in Table 6. Twenty four patients (49%) had a family history of premature (<35 years) sudden death (n=14, 29%) or ARVC (n=10, 20%). Thirty three patients had a history of palpitations (67%); 13 (27%) of syncope and 5 (10%) of cardiac arrests. Eleven patients (22%) experienced a previous sustained ventricular tachycardia (VT).

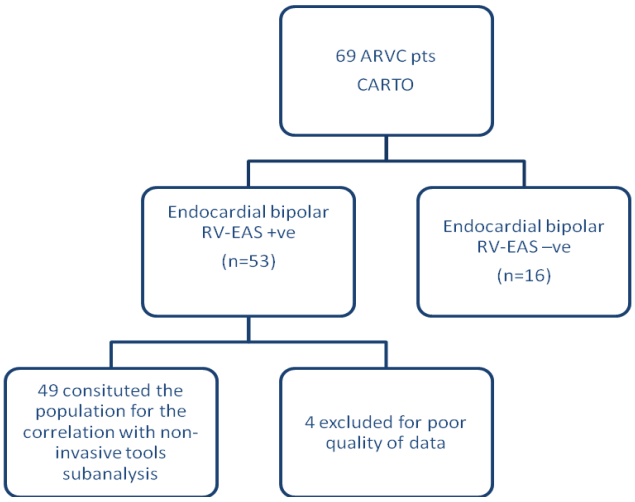


Figure 24. A breakdown of the study population.

ARVC: Arrhythmogenic right ventricular cardiomyopathies; RV-EAS: right ventricular electroanatomical scar.

Table 6 – Baseline clinical characteristics of the sub-analysis sample.

Males	38 (77)
Age (years)	35 (28-46)
Family history	
Sudden death	14 (29)
ARVC	10 (20)
Personal history	
Palpitations	33 (67)
Syncope	13 (27)
Sustained VT episodes	11 (22)
Cardiac arrest	5 (10)
24-Hour ECG-Holter	
Frequent (500/day) PVBs	42 (86)
Non-sustained VT (> 2 PVBs)	30 (61)
ECG abnormalities	
Left axis deviation	8 (16)
Right axis deviation	6 (12)
S wave > 60 msec in V1-V3	19 (39)
Low QRS voltages	14 (29)
QRS duration > 110 mses	21 (43)
Epsilon Waves	10 (20)
Negative T-waves*	32/46 (70)
Late potentials on SAECG	30 (61)
Echocardiographic findings	
RV end-diastolic volume (ml/m^2)	80 (63-96)
RV fractional area change (%)	30 (28-40)
LV end-diastolic volume (ml/m^2)	59 (56-61)
LV ejection fraction (%)	62 (55-73)

Results are shown as n (%) or as median (25-75iles). * 3 patients with complete right bundle branch block were excluded. EBM=endomyocardial biopsy; PVBs=premature ventricular beats; LV=left ventricle; RV=right ventricle; SAECG=signal averaged ECG; VT=ventricular tachycardia.

At 24-hour ECG-Holter monitoring, frequent (> 500/day) premature ventricular beats were documented in 42 (86%) patients and non-sustained VT (> 3 ventricular ectopic beats) in 30 patients (61%). Thirty four patients had undergone endomyocardial biopsy with fibrofatty replacement documented in 24 (71%).

12-lead ECG and SAECG

Twelve-lead ECG was completely normal in 5 (10%) individuals. The other 44 (90%) patients showed the following ECG abnormalities: left axis deviation (n=8, 16%); right axis deviation (n=6, 12%); complete right bundle branch block (n=3, 6%); S wave >60 msec (n=19, 39%); low QRS voltages (n= 14, 29%); QRS duration >110 msec (n=21, 43%) and epsilon waves (n=10, 20%). Negative T waves were recorded in 32/46 (70%) patients and showed the following distribution: 1) right precordial leads (V1-V3) in 8 (17%) patients, 2) right precordial leads extending to lateral precordial leads (V4-V6) in 11 (24%),and 3) both precordial (V2-V6) and inferior leads in 13 (28%). The presence of late potentials on SAECG was documented in 30 (61%) patients.

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Endocardial Voltage Mapping

High-density EVM was successfully acquired during sinus rhythm in all patients, with a median number of sites sampled of 203 (182-210). All patients showed ≥1 dense EAS (bipolar signal amplitude of endocardial electrograms <0.5 mV), which appeared sharply demarcated and typically surrounded by a

border zone with reduced signal amplitudes (0.5 to 1.5 mV). The median extent of total RV-EAS (including both dense scar and border zone) was 33 cm2 (12.4-67.8) corresponding to a median 22.5% (5.5-31.7%) of the total RV area. The involved RV regions were the infero-basal in 48 (98%) patients, the antero-lateral in 27 (55%), the RV outflow tract in 23 (47%) and the apical in 15 (31%).

Correlation of results

Correlation between echocardiographic EVM and echocardiographic findings are shown in figure 25. There was a significant correlation between the degree of right ventricular dilation/dysfunction and the RV-EAS % area. Correlation between ECG abnormalities and the RV-EAS% area is shown in Table 7. All 5 (10%) patients with a normal ECG had an RV-EAS area <10%. At univariate analysis, the presence of epsilon waves and negative T-waves were associated with a statistically significant greater RV-EAS% area. There was a significant correlation between the extent of negative T-waves across the ECG 12 leads and the RV-EAS% area (p for trend <0.001) (Figure 26). Normal T-waves were associated with a median EAS% area of 4.9% (4.5-6.4), negative T-waves in V1-V3 of 22.0% (8.5-30.6), negative T-waves in V1-V3 extending to lateral precordial leads (V4-V6) of 26.8% (11.5-35.2) and negative T-waves in both precordial (V2-V6) and inferior leads of 30.2% (24.8-33.0) (p for trend <0.001). The extent of negative T-waves across 12 leads was also significantly associated with both RV-EDV (p=0.01) and RV-FAC (p=0.01) (Table 8).

At multivariate analysis, after adjustment for the presence of epsilon waves, RV-EDV and RV-FAC, the extent of negative T-waves remained the only independent predictor of RV-EAS% area (B=4.4, 95% CI 1.3-7.4, p=0.006) (Table 9). Representative cases encompassing the spectrum of ECG repolarization abnormalities and EVM findings are shown in figure 27.

The analysis of correlation between ECG abnormalities and EAS involvement of specific RV regions showed a statistically significant association between 1) the presence of negative T-waves in the inferior

leads with the involvement of the RV infero-basal area (p=0.008) and 2) the presence of late potentials at SAECG with the involvement of the RV outflow tract (p=0.01).

Table 7 – Differences of percentage right ventricular electroanatomic scar according to the presence or absence of major ECG abnormalities and late potentials.

	RV-EAS area %		
ECG abnormalities	Yes	No	P
Left axis deviation	18.9 (10.3-33.8)	24.8 (5.4-31.7)	0.98
Right axis deviation	20.4 (4.9-32.8)	23.8 (8.8-31.8)	0.87
S wave > 60 msec	24.8 (5.6-31.6)	14.8 (7.9-31.9)	0.88
Low QRS voltages	30.8 (8.1-33.9)	19.1 (5.1-31.4)	0.34
dQRS > 110 mses	28.9 (11.0-33.0)	12.3 (5.1-31.4)	0.14
Epsilon waves	30.0 (10.1-37.0)	15.6 (5.1-27.8)	0.04
Negative T-waves*	29.6 (13.1-32.2)	4.9 (4.5-6.4)	<0.001
Late potentials on SAECG	29.6 (10.3-31.7)	10.6 (5.1-32.2)	0.30

* 3 patients with complete right bundle branch block were excluded

SAECG=signal averaged ECG

Table 8 – Correlation between extent of negative T-waves and right ventricular dilation/dysfunction.

	No NTW	NTW in V1-V3	NTW beyond V3	NTW in precordial and inferior leads	P
RV-EDV (ml/m^2)	65 (55-80)	75 (59-80)	84 (72-118)	97 (75-104)	0.01
RV-FAC (%)	40 (35-42)	35 (33-40)	31 (30-35)	32 (27-39)	0.01

FAC=fractional area change; EDV=end-diastolic volume; NTW=negative T-waves; RV=right ventricular

Table 9 – Multivariate analysis for predictors of RV-EAS% area

	B (95% C.I.)	p
Epsilon waves	2.9 (-5.4 - 11.2)	0.49
Extent of NTW	4.4 (1.3 - 7.4)	0.006
RV-EDV (ml/m^2)	0.04 (-0.2 – 1.4)	0.63
RV-FAC (%)	-0.7 (-1.4 – 0.2)	0.09

FAC=fractional area change; EDV=end-diastolic volume; NTW=negative T-waves; RV=right ventricular

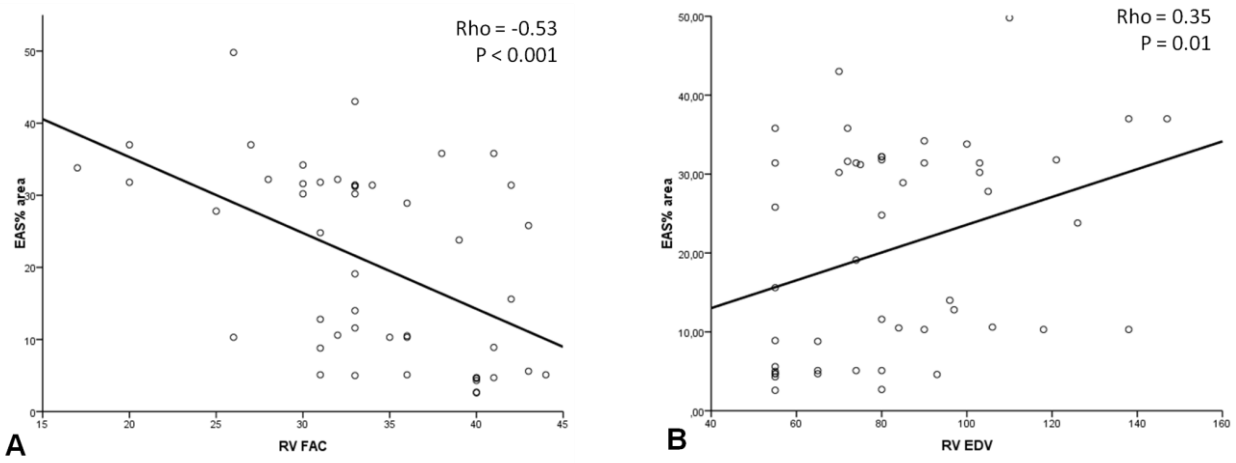

Figure 25: **(A)** Correlation between right ventricular fractional area change (RV FAC) and amount of RV EAS size (EAS% area). **(B)** Correlation between right ventricular end diastolic volume (RV EDV) and EAS% area.

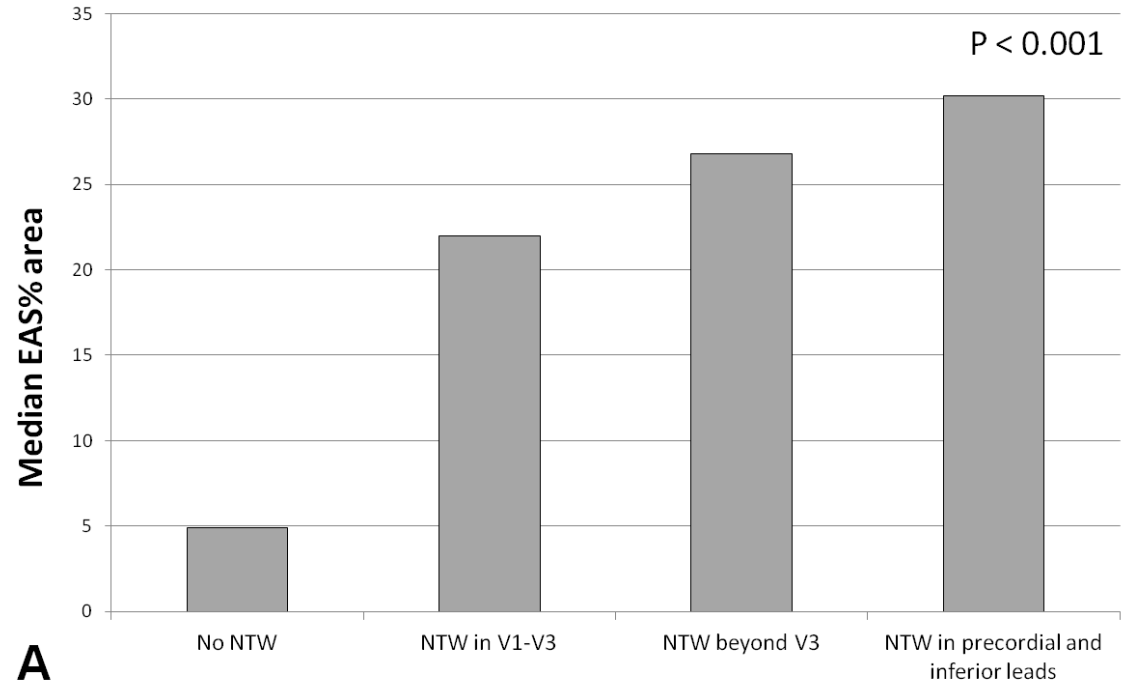

Figure 26. Correlation between extent of negative T-waves (NTW) and amount of right ventricular electroanatomical scar size

Follow-up

During a median follow-up of 36 (20-51) months, 18 patients (37%) experienced major arrhythmic events including sudden death (n=1), sustained ventricular tachycardia (n=11) and appropriate ICD intervention on ventricular tachycardia/fibrillation (n=7). Figure 28 shows the Kaplan-Meier analysis of survival from major arrhythmic events stratified by the extent of negative T-waves. All 5 patients with a normal ECG had an uneventful outcome.

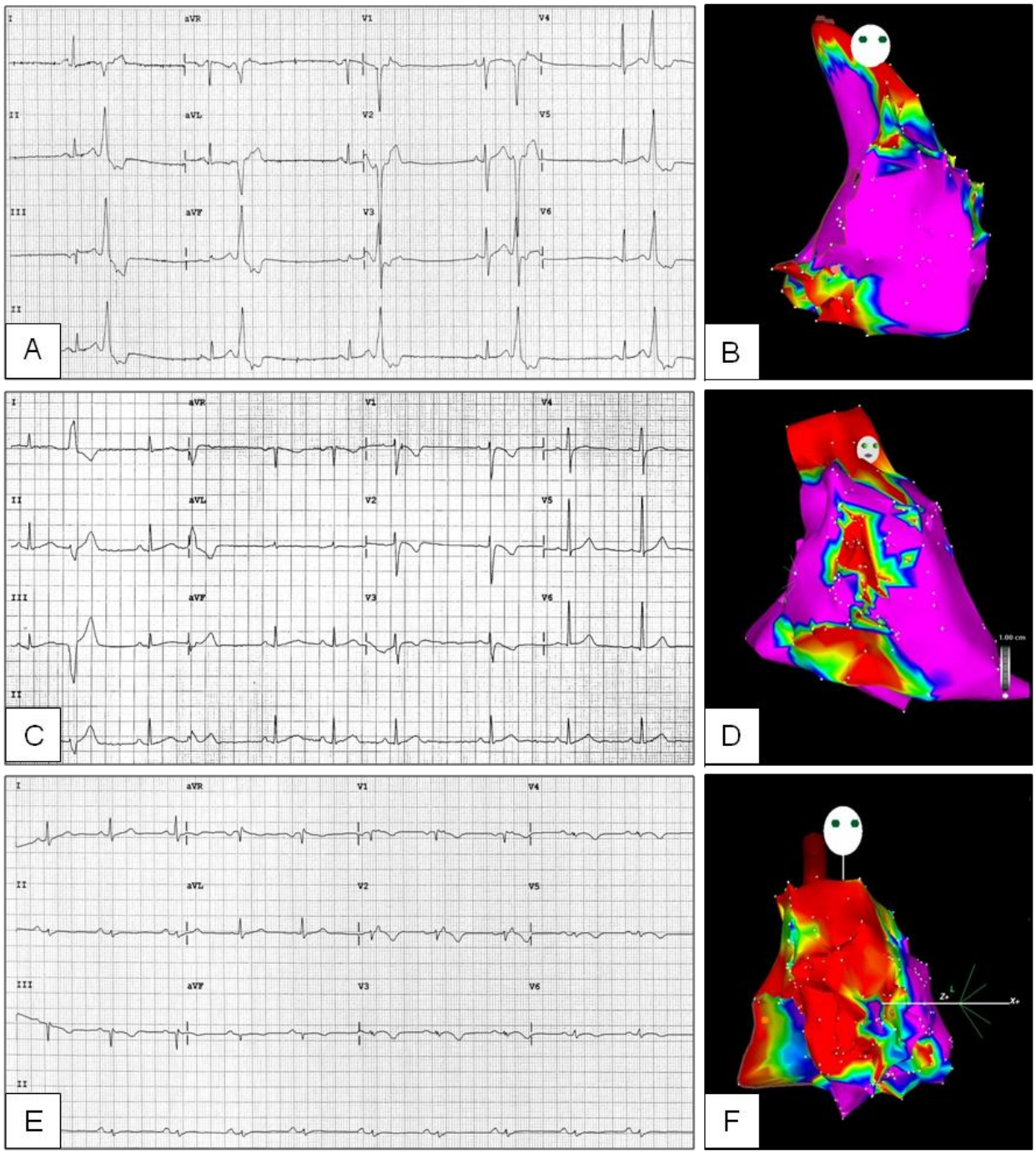

Figure 27. Representative cases of ARVC patients encompassing the spectrum of electrocardiographic (ECG) repolarization abnormalities and endocardial voltage mapping (EVM) findings.

(**A**) twelve-lead ECG of patient #21showing no repolarization abnormalities.

(**B**) Right oblique anterior view of EVM showing segmental right ventricular electroanatomic scars (RV-EAS) involving the inferobasal and outflow tract regions with replacement of the 8.4% of the RV.

(**C**) twelve-lead ECG of patient #5 showing T-wave inversion in V1-V3.

(**D**) Right oblique anterior view of EVM showing a total RV-EAS of 19.4% which involves the inferobasal, anterolateral and outflow tract regions.

(**E**) twelve-lead ECG of patient #21showing T-wave inversion in V1-V6, L2, L3 and aVF and epsilon waves in V1, V2.

(**F**) Anteroposterior view of EVM showing a total RV-EAS of 68.1% which myocardial substitution of the inferobasal, anterolateral, outflow tract and apical regions.

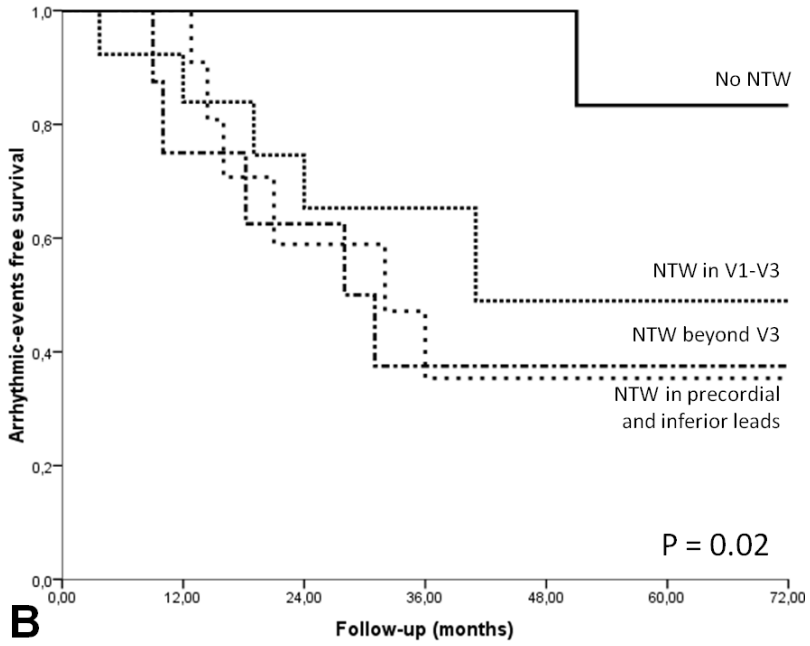

Figure 28. Kaplan-Meier analysis of survival from major arrhythmic events according to the extent of negative T-waves.

Effects of exercise on right precordial negative T waves in arrhythmogenic right ventricular cardiomyopathy

Methods

Study population

The study sample included 35 consecutive ARVC patients undergoing exercise testing at the time of first clinical evaluation during the period 2010-2012. All patients underwent comprehensive clinical evaluation including family and personal history, ECG, signal-averaged ECG (SAECG), 24-hour ECG Holter monitoring, exercise testing, echocardiogram and cardiac magnetic resonance. Technical equipment, protocols, and reference values are similar to those reported in Cohort 1.

Patients were enrolled in the study if 1) they fulfilled the criteria (2 major criteria, 1 major criteria plus 2 minor criteria or 4 minor criteria) for definite diagnosis of ARVC according to the 2010 Revised Task Force criteria (11), 2) showed negative T-waves in right precordial leads (V1-V3) and 3) were not undergoing beta-blockers or anti-arrhythmic drugs at the time of exercise testing.

Exercise test

All subjects underwent maximal bicycle exercise testing at the time of first clinical evaluation according to a protocol of 25-50 watt increments every 3 minutes. Twelve-lead ECG, heart rate and blood pressure were recorded at baseline, during the third minute of each exercise stage, at peak exercise and every 3 minutes into recovery. Criteria for interrupting the test were target heart rate (220 minus age), complex ventricular arrhythmias, hypotension, symptoms or exhaustion. The ECG patterns of right precordial negative T-waves in response to exercise were classified as *persistence of T-wave inversion* i.e.

no or minor (<50%) changes of negative T-waves amplitude; *T-wave normalization* i.e. negative T-wave becoming upright with exercise; and *partial reversal* when there was a positive increased in the T-wave amplitude ≥50% in ≥2 contiguous leads.

Control group

A group of 41 healthy subjects, with age and gender comparable to the ARVC study patients served as controls. They exhibited right precordial negative T-waves with no ST-segment elevation on ECG obtained at pre-participation screening and underwent the same comprehensive cardiovascular study protocol including exercise testing.

Statistical analysis

Categorical differences between groups were evaluated by the χ^2 test or the Fisher exact test as appropriate. Continuous variables were expressed as mean ± standard deviation and compared with Student's T-Test or with the Rank sum test as appropriate. Normal distribution of continuous variables was assessed by the Kolmogorov-Smirnov test. A value of $P<0.05$ was considered significant. Statistics were analyzed with SPSS version 17 (SPSS Inc, Chicago, Ill).

Results

Clinical characteristics

ARVC patients

The study population included 35 ARVC patients (19 males, mean age 22.2±6.2 years). Four patients (11%) had a positive family history for sudden cardiac death and 9 (26%) for ARVC. At the time of first clinical evaluation, 19 (54%) patients were symptomatic for palpitations, 4 (11%) for chest pain and 8

(23%) for syncope. Seven (20%) individuals experienced a previous sustained ventricular tachycardia (VT) and 1 (3%) suffered cardiac arrest due to ventricular fibrillation. At baseline ECG, 8 (23%) exhibited epsilon waves, 11 (31%) low voltages in limb leads and 15 (43%) a S wave >50 msec in V1. Negative T-waves extended beyond V3 in 17 (49%) patients. Late potentials on SAECG were demonstrated in 21 (60%) patients. On 24-hour Holter monitoring, frequent (≥500/24 hours) premature ventricular beats in 27 (77%) patients and non-sustained VT in 22 (63%). Morpho-functional right ventricular (RV) abnormalities, either global or regional, were documented at echocardiography in all patients; left ventricular (LV) dilatation/dysfunction was identified in 7 patients (20%).

Mean RV end-diastolic area was 28.0±6.0 cm^2, mean RV fraction area change was 35.4±8.6%, mean LV end-diastolic volume was 61.8±10.1 ml/m^2 and mean LV ejection fraction was 57.4±7.2%.

Control group

All 41 athletes (26 males, mean age 19.5±9.2 years) were asymptomatic, had a negative family history and showed no evidence of structural heart disease, late potentials or ventricular arrhythmias.

Exercise testing

ARVC patients

At peak of exercise, the patients reached a mean power of 162±43 watts, a mean heart rate of 168.8±23.9 beats per minute (bpm) (83.6±12.6% of target heart rate) and a double product (systolic blood pressure x heart rate) of 27643±6361 bpm x mmHg. Reasons for interruption were target heart rate in 20 (57%) patients and physical exhaustion in 15 (43%). On resting electrocardiogram, deepest negative T-wave in the right precordial leads had a mean amplitude of 0.41±0.14 mV and was observed more often in lead V2 (27/35, 77%). Right precordial negative T-waves persisted with exercise in 3 (9%) patients, normalized in 12 (34%) and partially reverted in 20 (57%). T-waves became positive or less negative at a mean power of 110±14 watt and gradually returned to baseline during the post-exercise phase. Representative cases of

response to exercise of right precordial repolarization abnormalities and ventricular arrhythmias are shown in Figure 29. One patient showed significant ST-segment depression at peak of exercise: he underwent myocardial perfusion scintigraphy that excluded an underlying myocardial ischemia. Ventricular arrhythmias were induced or increased by exercise in 10 (29%) ARVC patients and reduced or suppressed in 15 (42%); in the remaining 10 subjects (29%) no arrhythmias were observed thorough the exercise test.

Control group

At peak of exercise, the controls reached a mean power of 158±24 watts, a mean heart rate of 177.0±15.1 bpm (88.3%±7.2% of target heart rate) and a double product (systolic blood pressure x cardiac frequency) of 28314±4207 bpm x mmHg. Reasons for interruption were target heart rate in 26 (63%) and physical exhaustion in 15 (37%). No patients showed significant ST-segment depression at peak of exercise or ventricular arrhythmias at baseline or during exercise. Persistence of right precordial negative T-waves with exercise was observed in 5 (12%) controls, T-waves normalization in 23 (56%) and partial reversal in 13 (32%).

Correlation of results

ARVC patients

Correlation between changes of T-wave polarity and either clinical characteristics or exercise testing findings in ARVC patients are shown in Table 10 and 11. Patients with exercise-induced T-wave normalization were significantly younger (20.0±10.3 versus 28.7±8.4 years, p=0.03). There were no differences of exercise-induced right precordial T-wave pattern with regard to gender, personal and family history, echocardiographic and other ECG findings. Changes of negative T-waves at peak of exercise were independent from maximal power, heart rate, double product or reasons for test interruption.

Control group

There was no correlation between right precordial T-wave patterns and age, gender and exercise testing findings.

ARVC patients versus controls

There were no significant differences between controls and ARVC patients with regard to age, sex, maximal power, heart rate and double product at peak of exercise. The overall prevalence of right precordial T-waves changes with exercise (normalization *plus* partial reversal) was similar in ARVC patients and controls (92% versus 88%, p=1.00) while when we compared only complete normalization, there was a statistically non significant trend towards a higher prevalence in controls (59% versus 34%, p=0.06).

Table 10 – Comparison of clinical characteristics of ARVC patients (n=35) with and those without complete normalization of right precordial negative T waves at peak of exercise.

	Patients with normalization N=12	Patients without normalization N=23	P
Sex (male)	6 (50)	13 (57)	0.71
Age	20.0+10.3	28.7+8.4	0.03
Family history			
SD	1 (8)	3 (13)	1.0
ARVC	5 (42)	4 (17)	0.22
Personal history			
Palpitations	6 (50)	13 (57)	0.74

Chest pain	1 (8)	3 (13)	1.0
Syncope	1 (8)	7 (30)	0.22
Sustained VT	3 (25)	4 (17)	0.67
Cardiac arrest	1 (8)	0	0.34
ECG findings			
Epsilon waves	2 (17)	8 (35)	0.43
Low QRS voltage in limb leads	2 (17)	9 (39)	0.26
S wave >50 msec	3 (25)	12 (52)	0.17
Negative T-wave beyond V3	2 (17)	2 (9)	0.64
Maximal negative T-wave amplitude (mV)	0.39±014	0.42±0.13	0.73
Late potentials on SAECG	5 (42)	16 (70)	0.11
24-hour Holter monitoring			
≥500 PVB/24-hour	10 (83)	17 (74)	0.69
Non sustained VT	9 (75)	13 (57)	0.29
Echocardiographic findings			
RV end-diastolic area (cm^2)	27.6+5.7	28.2+7.2	0.80
RV fractional area change (%)	33.4±6.7	36.5±9.3	0.33
RV region WMA	10 (83)	21 (91)	0.59
LV end-diastolic volume (ml/mq)	59.2+8.9	63.0+10.6	0.31
LV ejection fraction (%)	58.0+4.5	57.1+8.3	0.75
LV region WMA	4 (33)	3 (13)	0.20

PVB=premature ventricular beats, LV=left ventricle; RV=right ventricle; SAECG=signal-averaged electrocardiogram; SD=sudden death; VT=ventricular tachycardia, WMA=wall motion abnormalities.

Table 11 – Comparison of results of exercise testing in patients with and those without complete normalization of right precordial negative T-waves at peak of exercise. Bpm=beats per minute, HR=heart rate, SBP=systolic blood pressure

	Patients with normalization N=12	Patients without normalization N=23	P
Peak of exercise			
Power (Watt)	177+42	155+43	0.25
HR (bpm)	164.3+25.8	156.1+23.1	0.36
HR*SBP (bpm*mmHg)	29722+4430	26782+6909	0.29
% target HR	85.0+11.1	82.1+13.4	0.87
Reasons for interruption			
Target frequency	8 (67)	12 (52)	0.72
Exhaustion	4 (33)	9 (48)	
Symptoms	0	0	
Hypotension	0	0	
ST-segment depression	0	1 (4)	1.0
Ventricular arrhythmias			
Absent	2 (17)	8 (35)	0.53
Induced/increased complexity	6 (50)	9 (39)	
Decreased complexity/suppressed	4 (33)	6 (26)	

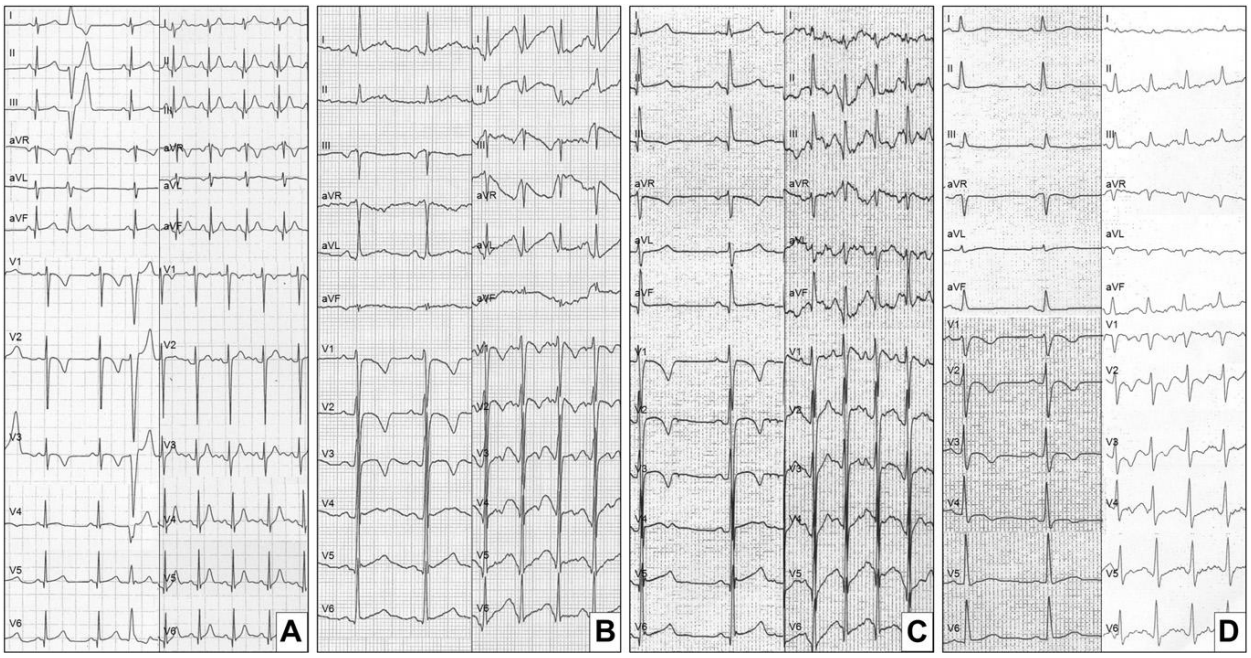

Figure 29. Representative cases of right precordial negative T-waves changes during exercise testing.

A) Patient #7: a 20 year-old female with negative T-wave in V1-V3 on baseline ECG both complete normalization of the T waves and suppression of ventricular arrhythmias occur at peak of exercise (125 watts, double product 23.960 bpm x mmHg) B) Patient #14: an 18 year-old male with negative T-wave in V1-V3 on baseline ECG and partial reversal of negative T-waves at peak of exercise (175 watts, double product 28.350 bpm x mmHg). C) Patient #20: a 25 year-old male with negative T-wave in V1-V3/V4 on baseline ECG and complete normalization of right precordial T-waves at peak of exercise (175 watts, double product of 30.200 bpm x mmHg). D) Patient#22: a 31 year-old male with negative T-wave in V1-V4 on baseline ECG and persistence of negative T-waves at peak of exercise (150 watts, double product of 26.840 bpm x mmHg

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DISCUSSION

The electrocardiogram is a crucial diagnostic and prognostic test, as it is readily available tool and can be extensively used in countries, like Egypt, where an ARVC program is still in its evolving phase (figure 30). In this work, we further studied some of the electrocardiographic features of ARVC. First, we proved that in comparison to other non-invasive tools, negative T waves present in the right and inferior leads correlate best with the presence and extent of RV EAS detected by endocardial voltage mapping in ARVC. Second, we demonstrated that these negative T waves are surrogate to RV EAS size as a prognosticator for arrhythmic risk in patients with ARVC. Finally, we specifically studied whether right precordial negative T waves of ARVC persist (or normalize) during exercise testing and whether that response to exercise may be a helpful diagnostic feature. Our results showed that there is no statistical difference in the rates of normalization of right precordial negative T waves observed with ARVC and those observed in controls.

Electrovoltage mapping as a diagnostic and a prognostic tool in ARVC

Endocardial voltage mapping is an emerging tool that has the ability to accurately identify and quantify RV regions with low-amplitude electric signals (i.e. EAS areas), which correspond to areas of fibrofatty myocardial replacement leading to loss of local electrical activity(5)(6)(7)(8)(9).

We evaluated the prognostic value of EVM in ARVC patients and showed that the presence and extent of abnormal RV bipolar-EVM was a powerful and independent predictor of arrhythmic risk. Moreover, EVM appeared to be superior to traditional arrhythmic risk factors, including RV dilation/dysfunction and inducibility of sustained ventricular tachycardia at programmed ventricular stimulation. Nevertheless, the routine use of EVM in ARVC patients for RV scar quantification and risk stratification is potentially limited because of its invasive nature, limited availability and high cost. Hence, it was crucial to evaluate

whether 12-lead ECG and SAECG allow non-invasive estimation of RV electrical lesions in ARVC patients.

ECG abnormalities in ARVC

Twelve-lead ECG is a fundamental part of the evaluation of ARVC patients. Inverted T-waves in right precordial leads, delayed S-wave upstroke, epsilon waves, low QRS voltages in limb leads and intra-ventricular conduction defects are the most striking ECG abnormalities in ARVC patients with an overt disease phenotype(10)(11)(12)(13). Accordingly, the present study showed that surface 12-lead ECG was abnormal in 90% of ARVC patients who had a diagnosis of definitive ARVC according to the 2010 International Task Force criteria and showed an abnormal EVM with evidence of ≥1 low amplitude areas. On the other hand, we found that patients with a normal ECG showed limited EAS involvement, a finding suggesting that the absence of ECG abnormalities reflects early/minor electrical disease of RV myocardium. Our findings are in agreement with those of Santangeli et al. who showed that an abnormal EVM was always associated with an abnormal ECG, although in their study a quantitative EAS area measurement and, thus, a correlation between ECG abnormalities and percentage of RV-EAS was not performed (120).

Negative T waves as surrogate for RV electroanatomic scar size

Previous studies demonstrated that T waves in ARVC typically become negative with the disease worsening and that greater extent of negative T waves across the ECG 12 leads is associated with more severe RV dilation and dysfunction(12)(13)(14). Our study results extend these previous observations by showing that negative T-waves allow to estimate the amount of EAS and contribute to predict the arrhythmic outcome of ARVC patients. The presence of ECG negative T waves was associated with a 6-times greater RV-EAS% area and the extent of negative T waves across ECG 12-leads was an independent predictor of RV-EAS size, regardless of the severity of RV dilation/dysfunction. The link

between repolarization abnormalities and the underlying EAS substrate was further substantiated by Kaplan-Meier analysis showing a statistically significant association between the extent of negative T waves and the occurrence of major arrhythmic events during follow-up. Over a long term follow-up, 53% of patients with negative T waves experienced sudden death, sustained ventricular tachycardia, or appropriate ICD interventions versus 7% of those without repolarization abnormalities.

The electrogenesis of negative T waves in ARVC

The electrogenesis of T waves inversion in ARVC and its relation with RV-EAS lesions remains to be elucidated. Based on our findings, one can speculate that replacement of RV myocardium by fibro-fatty tissue induces a ventricular electrical remodeling with changes of transmural and/or regional activation and repolarization times. These electrophysiological changes may become critical enough to cause reversal of repolarization gradients and lead to T-waves inversion on the ECG, with a "dose-effect" relationship between ECG repolarization abnormalities and electrical scar lesions.

Causes of negative T waves in the population

Causes of negative s on 12-lead ECG range from entirely benign conditions such as the persistent juvenile T-wave pattern to life-threatening disorders including coronary artery disease and cardiomyopathies.11 T-wave inversion is a normal feature of 12-lead ECG in pediatric age. During the first decade of life, changes of electrical predominance from the right ventricle (RV) to the left ventricle result in a gradual reversal of T-wave polarity, which progresses from left to right precordial leads as children grow older and leads after the puberty to the adult ECG pattern, characterized by negative T wave limited to V1. Persistence of T wave inversion in leads V1 to V2/V3 (known as persistence of the juvenile pattern of repolarization) may be observed in about 3% of healthy adults(15)(16)(19). In contrast, as earlier mentioned T wave inversion in right precordial leads is the most common ECG abnormality of ARVC, which is a recognized important cause of sudden cardiac death in young people and athletes (11)(12). Because clinical manifestations of ARVC usually occur after the puberty, the persistence of right

precordial T wave inversion (beyond V1) in the postpubertal age raises the problem of the differential diagnosis between a benign juvenile pattern of repolarization and a developing heart muscle disease.

Clinical work-up for negative T waves in sports screening

The clinical workup for differential diagnosis between pathologic and nonpathologic negative T waves traditionally includes electrocardiographic exercise testing. The current perspective is that negative T waves usually revert to normal with exercise in healthy subjects whereas they persist in patients with structural heart muscle disease(15). Changes of NTWs with exercise are considered a favorable feature supporting the benign nature of repolarization abnormalities(15)(121). However, the available data in favor of this concept are very limited. Serra-Grima et al studied 22 healthy athletes with NTWs at baseline ECG and observed in all cases a tendency to normalization during exercise. Pelliccia et al studied the clinical outcome of 81 elite athletes who exhibited marked repolarization abnormalities and a normal baseline echocardiogram. Five of 81 (6%) athletes developed many years later structural abnormalities consistent with a cardiomyopathy on serial echocardiographic exams. Exercise-induced partial or complete normalization of negative T waves with exercise had been observed in 58 of 76 (77%), whereas all athletes with a delayed occurrence of cardiomyopathy did not show any modifications of repolarization abnormalities during exercise testing(121)(122).

Value of exercise testing for negative T waves

A systematic study evaluating the changes of negative T waves with exercise has not been previously performed in patients with ARVC. Our study was designed to specifically assess whether right precordial negative T waves of ARVC persist (or normalize) during exercise testing and whether response to exercise may be a helpful diagnostic feature. We observed a complete normalization of right precordial NTWs with exercise in 34% of patients with ARVC and a trend toward normalization (i.e., either normalization or partial reversal) in 91%, figures similar to those observed in controls. Moreover, there

were no statistically significant differences between patients with ARVC with those without complete normalization of NTWs at peak of exercise with regard to disease phenotype such as symptoms, RV morphofunctional abnormalities, or ventricular arrhythmias.

Electrophysiological basis for exercise induced negative T wave changes

The electrophysiological mechanism underlying normalization of NTWs in ARVC remains to be elucidated. We may speculate that adrenergic stimulation may induce transient changes in transmural or regional activation times and also in the action potentials durations into the diseased RV myocardium. These changes, in a subgroup of patients with ARVC, can be critical enough to cause reversal of repolarization gradients leading to NTWs at baseline.

Clinical implications

The observation that right precordial NTWs normalize or tend to revert with exercise in most patients with ARVC has important clinical implications. It suggests that exercise induced changes of right precordial negative T waves do not add to the accuracy of clinical workup for differentiating between benign and cardiomyopathic repolarization abnormalities. Our results raise doubts about the current interpretation of NTWs normalization as a favorable exercise testing response, which may contribute to exclude an underlying cardiovascular disease with its inherent arrhythmic risk. Because in our study exercise-induced changes of NTWs were unrelated to ARVC phenotypic manifestations such as symptoms, RV morphofunctional abnormalities, or ventricular arrhythmias, they also appear of limited value for clinical and prognostic assessment of patients with ARVC.

Study limitations

Although both study cohorts were relatively large for ARVC, still a small number of patients and outcomes were analyzed, linked predominantly to relatively low disease prevalence, low event rate, and the low prevalence of negative T waves in general population. The small number of events limits both the power to detect associations and the ability to control completely for all potential confounders in the multivariable models. Nonetheless, we believe that our study results and statistical analysis indicate important trends that are of clinical relevance for the management of ARVC patients.

Also, the different rate of ICD implantation (54% of patients with an abnormal bipolar EVM versus 12% of those with normal bipolar EVM) may represent a study bias with regard to arrhythmia detection. However, ICD were routinely programmed to include a monitoring zone that identified VT with a rate >160 bpm; this lessens the potential limitation of not homogeneous distribution of ICD, because slower, asymptomatic VTs remained equally undetected in both patient subgroups, regardless of ICD monitoring.

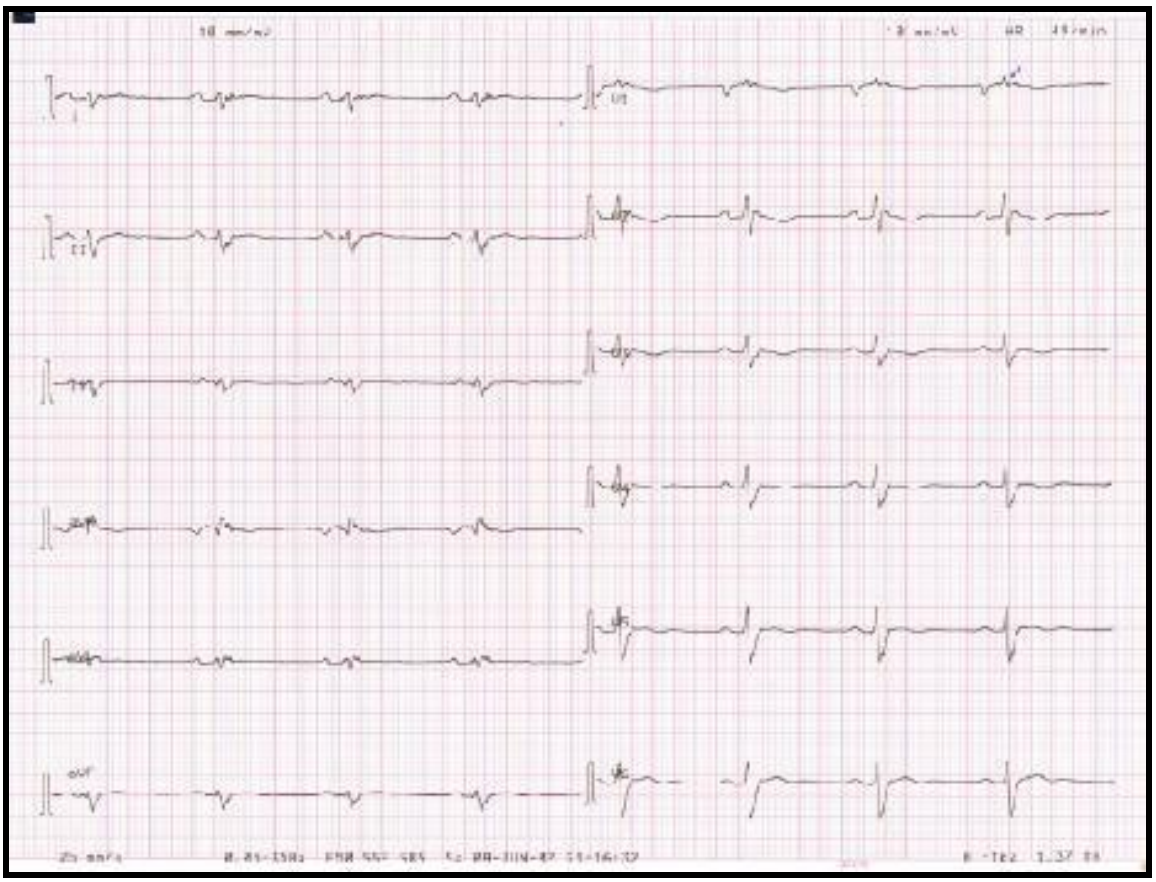

Figure 30. ECG of a 36 female Egyptian patient with ARVC. Note the negative T waves in V1-V5, the prolongation of activation from the nadir of S to the end of QRS complex, and the low voltage of QRS in limb leads.

REFERENCES

1. Thiene G, Nava A, Corrado D, Rossi L. Cardiomyopathy and sudden death in young people. New England Journal of Medicine. 1988;(318):129–33.

2. Basso C, Corrado D, Marcus FI, Nava A, Thiene G. Arrhythmogenic right ventricular cardiomyopathy. Lancet. 2009;373(9671):1289–300.

3. Corrado D, Basso C, Thiene G, McKenna WJ, Davies MJ, Fontaliran F, et al. Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multicenter study. Journal of the American College of Cardiology. 1997;30(6):1512–20.

4. Basso C, Thiene G, Corrado D, Angelini A, Nava A, Valente M. Arrhythmogenic right ventricular cardiomyopathy. Dysplasia, dystrophy, or myocarditis? Circulation. 1996;94(5):983–91.

5. Marchlinski FE, Zado E, Dixit S, Gerstenfeld E, Callans DJ, Hsia H, et al. Electroanatomic substrate and outcome of catheter ablative therapy for ventricular tachycardia in setting of right ventricular cardiomyopathy. Circulation. 2004; 19;110(16):2293–8.

6. Verma A, Kilicaslan F, Schweikert R a, Tomassoni G, Rossillo A, Marrouche NF, et al. Short- and long-term success of substrate-based mapping and ablation of ventricular tachycardia in arrhythmogenic right ventricular dysplasia. Circulation. 2005;111(24):3209–16.

7. Boulos M, Lashevsky I, Reisner S, Gepstein L. Electroanatomic mapping of arrhythmogenic right ventricular dysplasia. Journal of the American College of Cardiology. 2001;38(7):2020–7.

8. Corrado D, Basso C, Leoni L, Tokajuk B, Bauce B, Frigo G, et al. Three-dimensional electroanatomic voltage mapping increases accuracy of diagnosing arrhythmogenic right ventricular cardiomyopathy/dysplasia. Circulation. 2005;111(23):3042–50.

9. Corrado D, Basso C, Leoni L, Tokajuk B, Turrini P, Bauce B, et al. Three-dimensional electroanatomical voltage mapping and histologic evaluation of myocardial substrate in right ventricular outflow tract tachycardia. Journal of the American College of Cardiology. 2008;51(7):731–9.

10. Waller AD. A Demonstration on Man of Electromotive Changes accompanying the Heart's Beat. The Journal of physiology. 1887;8(5):229–34.

11. Einthoven W. Die galvanometrische registerung des menschlichen elektrokardiogram: zugleich eine beurtheilung der anwendung des capillarelektrometers in der physiologie. Pflugers Arch ges Physiol. 1903;1903:472–80.

12. Marcus FI, Abidov A. Arrhythmogenic right ventricular cardiomyopathy 2012: diagnostic challenges and treatment. Journal of cardiovascular electrophysiology. 2012 ;23(10):1149–53.

13. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke D a, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. European heart journal. 2010;31(7):806–14.

14. Steriotis AK, Bauce B, Daliento L, Rigato I, Mazzotti E, Folino AF, et al. Electrocardiographic pattern in arrhythmogenic right ventricular cardiomyopathy. The American journal of cardiology. 2009;103(9):1302–8.

15. Marcus FI, Zareba W. The electrocardiogram in right ventricular cardiomyopathy/dysplasia. How can the electrocardiogram assist in understanding the pathologic and functional changes of the heart in this disease? Journal of electrocardiology 2013;42(2):136.e1–5.

16. Nava A, Martini B, Thiene G, Buja GF, Canciani B, Scognamiglio R, et al. [Arrhythmogenic right ventricular dysplasia. Study of a selected population]. Giornale italiano di cardiologia. 1988;18(1):2–9.

17. Marcus FI. Prevalence of T-wave inversion beyond V1 in young normal individuals and usefulness for the diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia. The American journal of cardiology. 2005;95(9):1070–1.

18. Corrado D, Pelliccia A, Heidbuchel H, Sharma S, Link M, Basso C, et al. Recommendations for interpretation of 12-lead electrocardiogram in the athlete. European heart journal. 2010;31(2):243–59.

19. Suarez RM. The T-wave of the precordial electrocardiogram at different age levels. American heart journal. 1946;32(4):480–93.

20. Aro AL, Anttonen O, Tikkanen JT, Junttila MJ, Kerola T, Rissanen HA, et al. Prevalence and prognostic significance of T-wave inversions in right precordial leads of a 12-lead electrocardiogram in the middle-aged subjects. Circulation. 2012;125(21):2572–7.

21. Migliore F, Zorzi A, Michieli P, Perazzolo Marra M, Siciliano M, Rigato I, et al. Prevalence of cardiomyopathy in Italian asymptomatic children with electrocardiographic T-wave inversion at preparticipation screening. Circulation. 2012 Jan 24;125(3):529–38.

22. Lancisi GM. De motu cordis et anuerysmatibus. Neapoli (Italy): Musca; 1738.

23. Dalla Volta S, Battaglia G, Zerbini E. 'Auricularization' of right ventricular pressure curve. American heart journal. 1961;61:25–33.

24. Dalla Volta S, Fameli O, Maschio G. [The clinical and hemodynamic syndrome of auricularisation of the right ventricle. (Apropos of 4 personal cases)]. Archives des maladies du coeur et des vaisseaux. 1965;58(8):1129–43.

25. Thiene G. Arrhythmogenic cardiomyopathy: from autopsy to genes and transgenic mice (SCVP Achievement Award Lecture, San Antonio, TX, February 27, 2011). Cardiovascular pathology. 2012;21(4):229–39.

26. Marcus FI, Fontaine GH, Guiraudon G, Frank R, Laurenceau JL, Malergue C, et al. Right ventricular dysplasia: a report of 24 adult cases. Circulation. 1982;65(2):384–98.

27. Protonotarios N, Tsatsopoulou a, Patsourakos P, Alexopoulos D, Gezerlis P, Simitsis S, et al. Cardiac abnormalities in familial palmoplantar keratosis. British heart journal. 1986;56(4):321–6.

28. Nava a, Thiene G, Canciani B, Scognamiglio R, Daliento L, Buja G, et al. Familial occurrence of right ventricular dysplasia: a study involving nine families. Journal of the American College of Cardiology. 1988;12(5):1222–8.

29. Corrado D, Basso C, Rizzoli G, Schiavon M, Thiene G. Does sports activity enhance the risk of sudden death in adolescents and young adults? Journal of the American College of Cardiology. 2003;42(11):1959–63.

30. Elmaghawry M, Alhashemi M, Zorzi A, Yacoub MH. A global perspective of arrhythmogenic right ventricular cardiomyopathy. Global cardiology science & practice [Internet]. 2012;2012(2):81–92.

31. Sen-Chowdhry S, Morgan RD, Chambers JC, McKenna WJ. Arrhythmogenic cardiomyopathy: etiology, diagnosis, and treatment. Annual review of medicine. 2010;61:233–53.

32. Corrado D, Basso C, Thiene G, McKenna WJ, Davies MJ, Fontaliran F, et al. Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multicenter study. Journal of the American College of Cardiology. 1997;30(6):1512–20.

33. Sen-Chowdhry S, Syrris P, Prasad SK, Hughes SE, Merrifield R, Ward D, et al. Left-dominant arrhythmogenic cardiomyopathy: an under-recognized clinical entity. Journal of the American College of Cardiology. 2008;52(25):2175–87.

34. Basso C, Pilichou K, Carturan E, Rizzo S, Bauce B, Thiene G. Pathobiology of Arrhythmogenic Cardiomyopathy. Cardiac Electrophysiology Clinics. 2011;3(2):193–204.

35. Burke AP, Farb A, Tashko G, Virmani R. Arrhythmogenic right ventricular cardiomyopathy and fatty replacement of the right ventricular myocardium: are they different diseases? Circulation. 1998;97(16):1571–80.

36. Tabib a, Loire R, Chalabreysse L, Meyronnet D, Miras a, Malicier D, et al. Circumstances of death and gross and microscopic observations in a series of 200 cases of sudden death associated with arrhythmogenic right ventricular cardiomyopathy and/or dysplasia. Circulation. 2003;108(24):3000–5.

37. UHL HSM. A previously undescribed congenital malformation of the heart: almost total absence of the myocardium of the right ventricle. Bulletin of the Johns Hopkins Hospital [Internet]. 1952;91(3):197–209.

38. Calabrese F, Basso C, Carturan E, Valente M, Thiene G. Arrhythmogenic right ventricular cardiomyopathy/dysplasia: is there a role for viruses? Cardiovascular pathology. 2006;15(1):11–7.

39. d'Amati G, Di Gioia CR, Giordano C, Gallo P. Myocyte transdifferentiation: a possible pathogenetic mechanism for arrhythmogenic right ventricular cardiomyopathy. Archives of pathology & laboratory medicine. 2000;124(2):287–90.

40. Valente M, Calabrese F, Thiene G, Angelini A, Basso C, Nava A, et al. In vivo evidence of apoptosis in arrhythmogenic right ventricular cardiomyopathy. The American journal of pathology. 1998;152(2):479–84.

41. Yang Z, Bowles NE, Scherer SE, Taylor MD, Kearney DL, Ge S, et al. Desmosomal dysfunction due to mutations in desmoplakin causes arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circulation research. 2006;99(6):646–55.

42. Pilichou K, Remme CA, Basso C, Campian ME, Rizzo S, Barnett P, et al. Myocyte necrosis underlies progressive myocardial dystrophy in mouse dsg2-related arrhythmogenic right ventricular cardiomyopathy. The Journal of experimental medicine. 2009;206(8):1787–802.

43. Sato PY, Musa H, Coombs W, Guerrero-Serna G, Patiño GA, Taffet SM, et al. Loss of plakophilin-2 expression leads to decreased sodium current and slower conduction velocity in cultured cardiac myocytes. Circulation research. 2009;105(6):523–6.

44. Awad MM, Dalal D, Tichnell C, James C, Tucker A, Abraham T, et al. Recessive arrhythmogenic right ventricular dysplasia due to novel cryptic splice mutation in PKP2. Human mutation. 2006;27(11):1157.

45. Gerull B, Heuser A, Wichter T, Paul M, Basson CT, McDermott DA, et al. Mutations in the desmosomal protein plakophilin-2 are common in arrhythmogenic right ventricular cardiomyopathy. Nature genetics. 2004;36(11):1162–4.

46. Dalal D, James C, Devanagondi R, Tichnell C, Tucker A, Prakasa K, et al. Penetrance of mutations in plakophilin-2 among families with arrhythmogenic right ventricular dysplasia/cardiomyopathy. Journal of the American College of Cardiology. 2006;48(7):1416–24.

47. Hershberger RE, Cowan J, Morales A, Siegfried JD. Progress with genetic cardiomyopathies: screening, counseling, and testing in dilated, hypertrophic, and arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circulation. Heart failure. 2009;2(3):253–61.

48. Awad MM, Calkins H, Judge DP. Mechanisms of disease: molecular genetics of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Nature clinical practice. Cardiovascular medicine. 2008;5(5):258–67.

49. Xu T, Yang Z, Vatta M, Rampazzo A, Beffagna G, Pilichou K, et al. Compound and digenic heterozygosity contributes to arrhythmogenic right ventricular cardiomyopathy. Journal of the American College of Cardiology. 2010;55(6):587–97.

50. Klauke B, Kossmann S, Gaertner A, Brand K, Stork I, Brodehl A, et al. De novo desmin-mutation N116S is associated with arrhythmogenic right ventricular cardiomyopathy. Human molecular genetics. 2010;19(23):4595–607.

51. Priori SG, Napolitano C, Tiso N, Memmi M, Vignati G, Bloise R, et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. Circulation. 2001;103(2):196–200.

52. Laitinen PJ, Brown KM, Piippo K, Swan H, Devaney JM, Brahmbhatt B, et al. Mutations of the cardiac ryanodine receptor (RyR2) gene in familial polymorphic ventricular tachycardia. Circulation. 2001;103(4):485–90.

53. Tester DJ, Kopplin LJ, Will ML, Ackerman MJ. Spectrum and prevalence of cardiac ryanodine receptor (RyR2) mutations in a cohort of unrelated patients referred explicitly for long QT syndrome genetic testing. Heart rhythm. 2005;2(10):1099–105.

54. Carvajal-Huerta L. Epidermolytic palmoplantar keratoderma with woolly hair and dilated cardiomyopathy. Journal of the American Academy of Dermatology. 1998;39(3):418–21.

55. Norgett EE, Hatsell SJ, Carvajal-Huerta L, Cabezas JC, Common J, Purkis PE, et al. Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. Human molecular genetics. 2000;9(18):2761–6.

56. Keller D, Stepowski D, Balmer C, Simon F, Guenthard J, Bauer F, et al. De novo heterozygous desmoplakin mutations leading to Naxos-Carvajal disease. Swiss medical weekly. 2012;142.

57. Protonotarios N, Tsatsopoulou A, Anastasakis A, Sevdalis E, McKoy G, Stratos K, et al. Genotype-phenotype assessment in autosomal recessive arrhythmogenic right ventricular cardiomyopathy (Naxos disease) caused by a deletion in plakoglobin. Journal of the American College of Cardiology. 2001;38(5):1477–84.

58. Marcus FI. Arrhythmogenic Cardiomyopathy Diagnostic Criteria: An Update. Cardiac Electrophysiology Clinics. 2011;3(2):217–26.

59. Den Haan AD, Tan BY, Zikusoka MN, Lladó LI, Jain R, Daly A, et al. Comprehensive desmosome mutation analysis in north americans with arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circulation. Cardiovascular genetics. 2009;2(5):428–35.

60. Bhuiyan ZA, Jongbloed JDH, Van der Smagt J, Lombardi PM, Wiesfeld ACP, Nelen M, et al. Desmoglein-2 and desmocollin-2 mutations in dutch arrhythmogenic right ventricular

dysplasia/cardiomypathy patients: results from a multicenter study. Circulation. Cardiovascular genetics. 2009;2(5):418–27.

61. Protonotarios N, Tsatsopoulou A. Naxos disease and Carvajal syndrome: cardiocutaneous disorders that highlight the pathogenesis and broaden the spectrum of arrhythmogenic right ventricular cardiomyopathy. Cardiovascular pathology. 2004;13(4):185–94.

62. McKenna WJ, Thiene G, Nava A, Fontaliran F, Blomstrom-Lundqvist C, Fontaine G, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society. British heart journal. 1994;71(3):215–8.

63. Fontaine G, Fontaliran F, Hébert JL, Chemla D, Zenati O, Lecarpentier Y, et al. Arrhythmogenic right ventricular dysplasia. Annual review of medicine. 1999;50:17–35.

64. Nasir K, Bomma C, Tandri H, Roguin A, Dalal D, Prakasa K, et al. Electrocardiographic features of arrhythmogenic right ventricular dysplasia/cardiomyopathy according to disease severity: a need to broaden diagnostic criteria. Circulation. 2004;110(12):1527–34.

65. Peters S, Trümmel M, Koehler B, Westermann KU. The value of different electrocardiographic depolarization criteria in the diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Journal of electrocardiology. 2007;40(1):34–7.

66. Cox MGPJ, Nelen MR, Wilde AAM, Wiesfeld AC, Van der Smagt JJ, Loh P, et al. Activation delay and VT parameters in arrhythmogenic right ventricular dysplasia/cardiomyopathy: toward improvement of diagnostic ECG criteria. Journal of cardiovascular electrophysiology. 2008;19(8):775–81.

67. Turrini P, Corrado D, Basso C, Nava A, Bauce B, Thiene G. Dispersion of ventricular depolarization-repolarization: a noninvasive marker for risk stratification in arrhythmogenic right ventricular cardiomyopathy. Circulation. 2001;103(25):3075–80.

68. Ellison KE, Friedman PL, Ganz LI, Stevenson WG. Entrainment mapping and radiofrequency catheter ablation of ventricular tachycardia in right ventricular dysplasia. Journal of the American College of Cardiology. 1998;32(3):724–8.

69. O'Donnell D, Cox D, Bourke J, Mitchell L, Furniss S. Clinical and electrophysiological differences between patients with arrhythmogenic right ventricular dysplasia and right ventricular outflow tract tachycardia. European heart journal. 2003;24(9):801–10.

70. Sanborn DMY, Picard MH. Echocardiography in Arrhythmogenic Cardiomyopathy. Cardiac Electrophysiology Clinics. 2011;3(2):245–53.

71. Yoerger DM, Marcus F, Sherrill D, Calkins H, Towbin JA, Zareba W, et al. Echocardiographic findings in patients meeting task force criteria for arrhythmogenic right ventricular dysplasia: new insights from the multidisciplinary study of right ventricular dysplasia. Journal of the American College of Cardiology. 2005;45(6):860–5.

72. Marcus FI, Zareba W, Calkins H, Towbin JA, Basso C, Bluemke DA, et al. Arrhythmogenic right ventricular cardiomyopathy/dysplasia clinical presentation and diagnostic evaluation: results from the North American Multidisciplinary Study. Heart rhythm . 2009;6(7):984–92.

73. Leibundgut G, Rohner A, Grize L, Bernheim A, Kessel-Schaefer A, Bremerich J, et al. Dynamic assessment of right ventricular volumes and function by real-time three-dimensional echocardiography: a comparison study with magnetic resonance imaging in 100 adult patients. Journal of the American Society of Echocardiography. 2010;23(2):116–26.

74. Kjaergaard J, Hastrup Svendsen J, Sogaard P, Chen X, Bay Nielsen H, Køber L, et al. Advanced quantitative echocardiography in arrhythmogenic right ventricular cardiomyopathy. Journal of the American Society of Echocardiography. 2007;20(1):27–35.

75. Teske AJ, Cox MG, De Boeck BW, Doevendans PA, Hauer RN, Cramer MJ. Echocardiographic tissue deformation imaging quantifies abnormal regional right ventricular function in arrhythmogenic

right ventricular dysplasia/cardiomyopathy. Journal of the American Society of Echocardiography. 2009;22(8):920–7.

76. Wichter T, Indik JH, Paul M. Ventricular Angiography in Arrhythmogenic Cardiomyopathy. Cardiac Electrophysiology Clinics. 2011 Jun;3(2):255–67.

77. Indik JH, Wichter T, Gear K, Dallas WJ, Marcus FI. Quantitative assessment of angiographic right ventricular wall motion in arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C). Journal of cardiovascular electrophysiology. 2008;19(1):39–45.

78. Tandri H, Calkins H. MR and CT imaging of Arrhythmogenic Cardiomyopathy. Cardiac electrophysiology clinics. 2011;3(2):269–80.

79. Bomma C, Rutberg J, Tandri H, Nasir K, Roguin A, Tichnell C, et al. Misdiagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Journal of cardiovascular electrophysiology. 2004;15(3):300–6.

80. Tandri H, Bomma C, Calkins H, Bluemke DA. Magnetic resonance and computed tomography imaging of arrhythmogenic right ventricular dysplasia. Journal of magnetic resonance imaging. 2004;19(6):848–58.

81. Jain A, Shehata ML, Stuber M, Berkowitz SJ, Calkins H, Lima JAC, et al. Prevalence of left ventricular regional dysfunction in arrhythmogenic right ventricular dysplasia: a tagged MRI study. Circulation. Cardiovascular imaging. 2010;3(3):290–7.

82. Marra MP, Leoni L, Bauce B, Corbetti F, Zorzi A, Migliore F, et al. Imaging study of ventricular scar in arrhythmogenic right ventricular cardiomyopathy: comparison of 3D standard electroanatomical voltage mapping and contrast-enhanced cardiac magnetic resonance. Circulation. Arrhythmia and electrophysiology. 2012;5(1):91–100.

83. Garcia FC, Bazan V, Zado ES, Ren J-F, Marchlinski FE. Epicardial substrate and outcome with epicardial ablation of ventricular tachycardia in arrhythmogenic right ventricular cardiomyopathy/dysplasia. Circulation. 2009;120(5):366–75.

84. Dalal D, Jain R, Tandri H, Dong J, Eid SM, Prakasa K, et al. Long-term efficacy of catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. Journal of the American College of Cardiology. 2007;50(5):432–40.

85. Haqqani HM, Marchlinski FE. Electroanatomic Mapping and Catheter Ablation of Ventricular Tachycardia in Arrhythmogenic Cardiomyopathy. Cardiac Electrophysiology Clinics. 2011;3(2):299–310.

86. Wichter T, Borggrefe M, Haverkamp W, Chen X, Breithardt G. Efficacy of antiarrhythmic drugs in patients with arrhythmogenic right ventricular disease. Results in patients with inducible and noninducible ventricular tachycardia. Circulation. 1992;86(1):29–37.

87. Wichter T, Paul TM, Eckardt L, Gerdes P, Kirchhof P, Böcker D, et al. Arrhythmogenic right ventricular cardiomyopathy. Antiarrhythmic drugs, catheter ablation, or ICD? Herz. 2005;30(2):91–101.

88. Marcus GM, Glidden D V, Polonsky B, Zareba W, Smith LM, Cannom DS, et al. Efficacy of antiarrhythmic drugs in arrhythmogenic right ventricular cardiomyopathy: a report from the North American ARVC Registry. Journal of the American College of Cardiology. 2009;54(7):609–15.

89. Link MS, Estes NAM. Arrhythmogenic Cardiomyopathy: Pharmacologic Management. Cardiac Electrophysiology Clinics. 2011;3(2):293–8.

90. Corrado D, Leoni L, Link MS, Della Bella P, Gaita F, Curnis A, et al. Implantable cardioverter-defibrillator therapy for prevention of sudden death in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. Circulation. 2003;108(25):3084–91.

91. Corrado D, Calkins H, Link MS, Leoni L, Favale S, Bevilacqua M, et al. Prophylactic implantable defibrillator in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and no prior ventricular fibrillation or sustained ventricular tachycardia. Circulation. 2010;122(12):1144–52.

92. Wichter T, Paul M, Wollmann C, Acil T, Gerdes P, Ashraf O, et al. Implantable cardioverter/defibrillator therapy in arrhythmogenic right ventricular cardiomyopathy: single-center experience of long-term follow-up and complications in 60 patients. Circulation. 2004;109(12):1503–8.

93. Kirchhof P, Fabritz L, Zwiener M, Witt H, Schäfers M, Zellerhoff S, et al. Age- and training-dependent development of arrhythmogenic right ventricular cardiomyopathy in heterozygous plakoglobin-deficient mice. Circulation. 2006;114(17):1799–806.

94. Corrado D, Basso C, Pavei A, Michieli P, Schiavon M, Thiene G. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. JAMA : the journal of the American Medical Association. 2006;296(13):1593–601.

95. Corrado D, Basso C, Schiavon M, Thiene G. Screening for hypertrophic cardiomyopathy in young athletes. The New England journal of medicine. 1998;339(6):364–9.

96. Shimizu M, Ino H, Okeie K, Yamaguchi M, Nagata M, Hayashi K, et al. T-peak to T-end interval may be a better predictor of high-risk patients with hypertrophic cardiomyopathy associated with a cardiac troponin I mutation than QT dispersion. Clinical cardiology. 2002;25(7):335–9.

97. Topilski I, Rogowski O, Rosso R, Justo D, Copperman Y, Glikson M, et al. The morphology of the QT interval predicts torsade de pointes during acquired bradyarrhythmias. Journal of the American College of Cardiology. 2007;49(3):320–8.

98. Watanabe N, Kobayashi Y, Tanno K, Miyoshi F, Asano T, Kawamura M, et al. Transmural dispersion of repolarization and ventricular tachyarrhythmias. Journal of electrocardiology. 2004;37(3):191–200.

99. Antzelevitch C. Role of spatial dispersion of repolarization in inherited and acquired sudden cardiac death syndromes. American journal of physiology. Heart and circulatory physiology. 2007;293(4):H2024–38.

100. Burdon-Sanderson J. On the Electrical Phenomena of the Excitatory Process in the Heart of the Frog and of the Tortoise, as investigated Photographically. The Journal of physiology. 1884;4(6):327–386.15.

101. Byliss W, Starling E. On the elctromotive phenomena of the mammalian heart. Monthly Int J anat physiol. 1892;256–81.

102. Mines GR. On functional analysis by the action of electrolytes. The Journal of physiology. 1913;46(3):188–235.

103. Wilson F, Macleod A, PS. B. The T deflection of the electrocardiogram. Trans Assoc Am Physicians. 1931;(46):46:29 –38.

104. Cohen I, Giles W, Noble D. Cellular basis for the T wave of the electrocardiogram. Nature [Internet]. 1976;262(5570):657–61.

105. Sicouri S, Antzelevitch C. A subpopulation of cells with unique electrophysiological properties in the deep subepicardium of the canine ventricle. The M cell. Circulation research. 1991;68(6):1729–41.

106. Sicouri S, Fish J, Antzelevitch C. Distribution of M cells in the canine ventricle. Journal of cardiovascular electrophysiology. 1994;5(10):824–37.

107. Antzelevitch C, Shimizu W, Yan GX, Sicouri S, Weissenburger J, Nesterenko V V, et al. The M cell: its contribution to the ECG and to normal and abnormal electrical function of the heart. Journal of cardiovascular electrophysiology. 1999;10(8):1124–52.

108. Yan GX, Antzelevitch C. Cellular basis for the electrocardiographic J wave. Circulation. 1996;93(2):372–9.

109. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. Circulation. 1998;98(18):1928–36.

110. Yan GX, Shimizu W, Antzelevitch C. Characteristics and distribution of M cells in arterially perfused canine left ventricular wedge preparations. Circulation. 1998;98(18):1921–7.

111. Patel C, Burke JF, Patel H, Gupta P, Kowey PR, Antzelevitch C, et al. Is there a significant transmural gradient in repolarization time in the intact heart? Cellular basis of the T wave: a century of controversy. Circulation. Arrhythmia and electrophysiology. 2009;2(1):80–8.

112. Opthof T, Coronel R, Janse MJ. Is there a significant transmural gradient in repolarization time in the intact heart?: Repolarization Gradients in the Intact Heart. Circulation. Arrhythmia and electrophysiology. 2009;2(1):89–96.

113. el-Sherif N, Caref EB, Yin H, Restivo M. The electrophysiological mechanism of ventricular arrhythmias in the long QT syndrome. Tridimensional mapping of activation and recovery patterns. Circulation research. 1996;79(3):474–92.

114. Taggart P, Sutton PM, Opthof T, Coronel R, Trimlett R, Pugsley W, et al. Transmural repolarisation in the left ventricle in humans during normoxia and ischaemia. Cardiovascular research. 2001;50(3):454–62.

115. Conrath CE, Wilders R, Coronel R, De Bakker JMT, Taggart P, De Groot JR, et al. Intercellular coupling through gap junctions masks M cells in the human heart. Cardiovascular research. 2004;62(2):407–14.

116. Franz MR, Bargheer K, Rafflenbeul W, Haverich A, Lichtlen PR. Monophasic action potential mapping in human subjects with normal electrocardiograms: direct evidence for the genesis of the T wave. Circulation. 1987;75(2):379–86.

117. Conrath CE, Opthof T. Ventricular repolarization: an overview of (patho)physiology, sympathetic effects and genetic aspects. Progress in biophysics and molecular biology. 2006;92(3):269–307.

118. Chauhan VS, Downar E, Nanthakumar K, Parker JD, Ross HJ, Chan W, et al. Increased ventricular repolarization heterogeneity in patients with ventricular arrhythmia vulnerability and cardiomyopathy: a human in vivo study. American journal of physiology. Heart and circulatory physiology. 2006;290(1):H79–86.

119. Antzelevitch C. Role of spatial dispersion of repolarization in inherited and acquired sudden cardiac death syndromes. American journal of physiology. Heart and circulatory physiology. 2007;293(4):H2024–38.

120. Santangeli P, Pieroni M, Dello Russo A, Casella M, Pelargonio G, Macchione A, et al. Noninvasive diagnosis of electroanatomic abnormalities in arrhythmogenic right ventricular cardiomyopathy. Circulation. Arrhythmia and electrophysiology. 2010;3(6):632–8.

121. Pelliccia A, Di Paolo FM, Quattrini FM, Basso C, Culasso F, Popoli G, et al. Outcomes in athletes with marked ECG repolarization abnormalities. The New England journal of medicine. 2008;358(2):152–61.

122. Serra-Grima R, Estorch M, Carrió I, Subirana M, Bernà L, Prat T. Marked ventricular repolarization abnormalities in highly trained athletes' electrocardiograms: clinical and prognostic implications. Journal of the American College of Cardiology. 2000;36(4):1310–6.

CURRICULUM VITAE

PERSONAL INFORMATION Mohamed Adel ElMaghawry

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Sex: Male | Date of birth 01/09/1979| Nationality Egyptian

WORK EXPERIENCE

2013-Today	Cardiology Specialist and Research Fellow
	Aswan Heart Centre, Aswan, Egypt
2012-2013	Cardiac Electrophysiology and Pacing Fellow/Observer
	University of Padua, Italy
	University of Brescia, Italy
2009-2012	Cardiology Assistant Specialist
	Aswan Heart Centre, Aswan, Egypt
2006-2009	Cardiology Resident
	National Heart Institute, Cairo, Egypt
2006-2011	Instructor of Advanced Life Support for Adults and Paediatrics

	European Resuscitation Council
	Egyptian Resuscitation Council
2005-2006	Critical Care Resident
	ElSahel Teaching Hospital, Cairo, Egypt

EDUCATION AND TRAINING

2012-2015	PhD in Cardiovascular Sciences-Candidate
	University of Padua, Italy
	Course Director: Professor Gaetano Thiene
	Supervisor: Professor Domenico Corrado
	(Advances in electrocardiographic features of arrhythmogenic right ventriuclar cardiomyopathy)
2010	Certified Cardiac Device Specialist (CCDS)
	International Board of Heart Rhythm Examiners, part of Heart Rhythm Society, USA
2006-2008	Masters Degree in Cardiovascular Medicine
	Ain Shams University, Cairo, Egypt
	Supervisor: Professor Mervat Abulmaaty
	(Characterization of pulmonary vein potentials recorded by lasso catheter in patients with paroxysmal atrial fibrillation)
2006	Diploma in Cardiac Electrophysiology

	Ain Shams University, Cairo, Egypt
1996-2002	Medical Doctorate
	Ain Shams University, Cairo, Egypt

PERSONAL SKILLS

Mother tongue	Arabic

Other language(s)	UNDERSTANDING		SPEAKING		WRITING
	Listening	Reading	Spoken interaction	Spoken production	
English	Excellent	Excellent	Excellent	Excellent	Excellent
French	Excellent	Excellent	Very Good	Very Good	Very Good
Italian	Good	Good	Good	Good	Basic

Communication , Managerial and Organizational skills

Responsible for establishing cardiac electrophysiology and pacing service at Aswan Heart Centre. Responsible for organizing training programs for junior cardiology fellows at Aswan Heart Centre.

Participant of clinical audit and governance at Aswan Heart Centre.

Participated in the organization of many conferences, volunteer work, and workshops during medical school and residency years. This includes many medical conferences, the Model United Nations and International Student Leadership Conferences at the American university in Cairo, and fund raising campaigns for neuropsychiatric department in ElSahel teaching hospital and for the pediatric intensive care unit in National Heart Institute, Cairo.

ACTIVITIES DURING PhD PERIOD

Publications

1. Zorzi A, **ElMaghawry M**, Corrado D. Evolving interpretation of the athletes electrocardiogram: From European Society of Cardiology and Stanford Criteria to Seattle Criteria and beyond. Journal of Electrocardiology (in press).
2. **ElMaghawry M**, ElMahdi MF. (2014). REVERSE 5-year follow up: CRT impact persists. Global Cardiology Scientific and Practice: Vol. 2014 3, 39. (e-pub ahead of print).
3. **ElMaghawry M**, ElGuindy A. (2014). STOP-HF: Expanding the role of HF programs into the community. Global Cardiology Science and Practice: Vol. 2014 2, 23. (e-pub ahead of print).
4. **ElMaghawry M**, Zanatta A, Zampieri F. The discovery of pulmonary circulation: From Imhotep to Harvey. Global Cardiology Science and Practice. 2014 Jun 18;2014(2):103-16.
5. Migliore F, Zorzi A, Spadotto V, **ElMaghawry M**, Tarantini G. Response to: Coronary artery systolic "milking" and "bridging" in Takotsubo syndrome: substrate or an epiphenomenon? Global Cardiology Science Practice. 2014 Jan 29;2014(1):100.
6. Elguindy AM, **ElMaghawry M**. Block HF: CRT gains new ground. Global Cardiology Science Practice. 2013 Dec 30;2013(4):361-3.
7. Bontempi L, Vassanelli F, Lipari A, Locantore E, Cassa MB, Salghetti F, **ElMaghawry M**, Vizzardi E, D'Aloia A, Mahmudov R, Cerini M, Curnis A. Extraction of a cronary sinus lead: always so easy? Journal of Cardiovascular medicine (Hagerstown) (epub ahead of print).
8. Salghetti F, Vizzardi E, **ElMaghawry M**, Mamedouv R, D'Aloia A, Bonadei I, Sciatti E, Lipari A, Cerini M, Bontempi L, Metra M, Curnis A. Need for ongoing anti arrhythmic drugs after ablation of atrial fibrillation. Review. Recent Pat Cardiovasc Drug Discov. 2013 Dec;8(3):204-15.

9. Zorzi, A, Migliore F, **ElMaghawry M**, Silvano M, Marra MP, Niero A, Nguyen K, Rigato I, Bauce B, Basso C, Thiene G, Iliceto S, and Corrado D, "Electrocardiographic Predictors of Electroanatomic Scar Size in Arrhythmogenic Right Ventricular Cardiomyopathy: Implications for Arrhythmic Risk Stratification.," Journal of cardiovascular electrophysiology, Jul. 2013.
10. Meggiolaro M, Zorzi A, **ElMaghawry M**, Peruzza F, Migliore F, and Pittoni GM, "Brugada ECG disclosed by acute malaria: is it all about fever and propofol?," Journal of clinical anesthesia, Aug. 2013.
11. Spadotto V, **Elmaghawry M**, Zorzi A, Migliore F, & Marra, MP, "Apical ballooning with mid-ventricular obstruction: the many faces of Takotsubo cardiomyopathy." Global Cardiology Science and Practice, 2013.
12. Zampieri F., Zanatta A., **Elmaghawry M**., Bonati M. R., & Thiene, G. "Origin and development of modern medicine at the University of Padua and the role of the "Serenissima" Republic of Venice." Global Cardiology Science and Practice, 2013.
13. Zorzi A, **ElMaghawry M**, Rigato I, Cardoso Bianchini F, Crespi Ponta G, Michieli P, Migliore F, Marra MP, Bauce B, Basso C, Schiavon M, Thiene G, Iliceto S, and Corrado D, "Exercise-induced normalization of right precordial negative T waves in arrhythmogenic right ventricular cardiomyopathy.," The American journal of cardiology, vol. 112, no. 3, pp. 411–5, Aug. 2013.
14. **ElMaghawry M**, Migliore F, Zorzi A, Bauce B, Leoni L,Bertaglia E, Iliceto S, and Corrado D. "Implantable Cardioverter-Defibrillator Therapy in Athletes." Cardiac Electrophysiology Clinics 5, no. 1 (2013): 123-130.
15. Zorzi A, **ElMaghawry M**, Migliore F, Rigato I, Basso C, Thiene G, and Corrado D. "ST-Segment Elevation and Sudden Death in the Athlete." Cardiac Electrophysiology Clinics 5, no. 1 (2013): 73-84.

16. Migliore F, Zorzi A, Silvano M, Bevilacqua M, Leoni L, Marra MP, **ElMaghawry M**, Brugnaro L, Dal Lin C, Bauce B, Rigato I, Tarantini G, Basso C, Buja G, Thiene G, Iliceto S, and Corrado D, "Prognostic value of endocardial voltage mapping in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia.," Circulation. Arrhythmia and electrophysiology, vol. 6, no. 1, pp. 167–76, Feb. 2013.

17. Spadotto V, Zorzi A, **ElMaghawry M**., Meggiolaro,M., & Pittoni G. M. (2013). Heart failure due to 'stress cardiomyopathy': a severe manifestation of the opioid withdrawal syndrome. European Heart Journal: Acute Cardiovascular Care, 2(1), 84-87.

18. Bontempi, L., Vassanelli F, Lipari A, Pagnoni C, Locantore E, **ElMaghawry M**, Salghetti F, Cerini M, and Curnis A, "[Role of antiarrhythmic therapy for atrial fibrillation]." Giornale italiano di cardiologia (2006) 14, no. 3 (2013): 76-81.

19. **ElMaghawry M**, Migliore F, Nazar M, Sandou D, and Alhashemi M. "Science and practice of arrhythmogenic cardiomyopathy: A paradigm shift." Global Cardiology Science and Practice 2013 (2012).

20. **ElMaghawry M**, Alhashemi M, Zorzi A, and Yacoub M, "A global perspective of arrhythmogenic right ventricular cardiomyopathy." Global Cardiology Science and Practice 2012 (2012).

21. Pistollato E, Zorzi A, **ElMaghawry M**, Gasparetto N, Cacciavillani L, and Bortoluzzi A, "Thrombolysis during resuscitation: should we focus on sudden cardiac arrest after myocardial infarction?," Resuscitation, vol. 83, no. 9, pp. e189–90, Sep. 2012.

22. **ElMaghawry M**., Zorzi, A., Marra, M. P., and Corrado, D. (2012). Life saving pre-participation athletic screening. Heart and metabolism, (56), 29-33.

Abstracts

1. Prognostic value of unipolar vs bipolar electroanatomic voltage mapping in patients with ARVC/D. II International Symposium on Advances on Cardiomyopathies - 9th meeting of the European myocardial and pericardial diseases WG of the ESC. Florence September 2012
2. ARVC and pregnancy: influence and clinical course. II International Symposium on Advances on Cardiomyopathies - 9th meeting of the European myocardial and pericardial diseases WG of the ESC. Florence September 2012
3. Thrombolysis for myocardial infarction complicated with refractory cardiac arrest. 7th European Emergency Medicine Conference. Antalya, Turkey , October 2012
4. Thrombolysis during CPR in the emergency department for confirmed myocardial infarction. European resuscitation council conference. Vienna, Austria, October 2012
5. Reimplantation of LV lead after extraction. 15th International symposium on clinical pacing. Rome, December 2012
6. Prevalence and management of acute life-threatening arrhythmias in Tako tsubo cardiomyopathy. 73 Congresso nazionale della societe italiana di cardiologia. Rome, December 2012
7. Prognostic value of unipolar vs bipolar voltage mapping in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. 73 Congresso nazionale della societe italiana di cardiologia. Rome, December 2012
8. Correlazione tra pattern ECG di Wellens (inversione dell'onda T e allungamento del QT) e edema miocardico nella sindrome Takotsubu.73 Congresso nazionale della societe italiana di cardiologia. Rome, December 2012

9. Single centre experience with permanent transvenous lead extraction: analysis on factors influencing the difficulty of the procedure. European Cardiac Arrhythmia Society 9th conference. Paris, France, March 2013

10. Usefulness of a new enhanced excimer laser technique 80 Hz for leads extraction: a single centre experience. European Cardiac Arrhythmia Society 9th conference. Paris, France, March 2013

11. Transvenous extraction of PM and ICD leads in infective endocarditis with vegetations: A single centre experience. European Cardiac Arrhythmia Society 9th conference. Paris, France, March 2013

12. Esperienza di un singolo centro sull'estrazione di cateteri endovenosi permanenti: analisi dei fattori che influenzano la difficolta' della procedura. 10th AIAC congress, Bologna, March 2013

13. Efficacia dell'isolamento delle vene polmonari mediante tecnica cryo: risultati a medio termine di un singolo centro. 10th AIAC congress, Bologna, March 2013

14. A comparison between lead extraction results using 80 Hz and 40 Hz laser-powered sheaths. EHRA EUROPACE 2013, Athens, Greece, June 2013

15. Efficacy and safety of pulmonary vein isolation with cryo technique. 4th international society for pharmacoeconomics and outcome research (ISPOR). Buenos Aires, Argentina, September 2013

16. Permanent transvenous lead extraction: factors influencing difficulty of the procedure. . 4th international society for pharmacoeconomics and outcome research (ISPOR). Buenos Aires, Argentina, September 2013

Lectures

1. Cardiac pacing and ICD in hypertrophic cardiomyopathy. Ain Shams University. Cairo, Egypt. December 2012.
2. Ibn an –Nafis and the Discovery of Pulmonary Circulation . Clinico –pathological conference. Padua, Italy. March 2013
3. Tissue characterization of arrhythmogenic right ventricular cardiomyopathy. Erice, Italy. Novembre 2013.
4. Echocardiographic features of ARVC. Egyptian Society of Cardiology International Conference. Cairo, Egypt. May 2014.
5. Arrhythmogenic right ventricular cardiomyopathy: SCD risk stratification. Ain Shams University, Cairo, Egypt. November 2013.
6. Basic electrophysiology and cardiac pacing lectures. Aswan Heart Centre continuous medical education program. Aswan, Egypt. Jan-Dec 2014.
7. Echocardiographic features of ARVC. Egyptian Society of Cardiology International Conference. Cairo, Egypt. May 2014
8. History of pulmonary circulation. Aswan Heart centre , Aswan, Egypt. June-2014.
9. Residual Cardiovascular Risk. Cardiolipid conference. Hurgada, Egypt. November 2014

Congresses and courses attended

1. Clinicopathology conferences, Padova, 2012-2013
2. University of Padua celebrating 300 years of Morgagni/Morgagni lectures, Padova 2012
3. Cardiovascular pathology lectures, Prof. Thiene, Prof.ssa Angelini, Prof.ssa Basso 2012-2013
4. Arrhythmia lectures, Prof. Corrado, Padova. 2012-2013
5. Congenital cardiac defects pathology lectures, Prof.ssa Frescura. 2012
6. Cardiac resynchronization therapy and implantable cardioverter defibrillators courses, Prof. Curnis, Brescia. 2012-2013.
7. Lead extraction courses, Prof. Curnis, Brescia
8. Anatomy for the arrhythmologists, 2012-2013
9. Spring school, Bressanone, March 2012
10. Pediatric cardiology and cardiothoracic surgery conference, Padova, April 2012
11. Basic course on pediatric echocardiography, Padova, April 2012
12. Invasive electrophysiology conference (Veneto area), Padova, May 2012
13. Atrial fibrillation ablation conference (Veneto area), Villa Braida, September 2012
14. Summer School, Padova September 2012
15. Cardiac pacing and ICD EHRA course. Vienna, Austria, March 2014.
16. Fellow course in cardiovascular interventions. Cardiovascular Research Foundation. Las Vegas, USA, May 2014
17. Advanced course on VT ablation. San Rafael, Milan, Italy. September 2014

Research and clinical activites

- Training in cardiac electrophysiology and cardiac devices. University of Padua, Padua, Italy under the supervision of Professor Domenico Corrado.
- Training in cardiac electrophysiology and cardiac devices. University of Brescia, Brescia, Italy under the supervision of Professor Antonio Curnis.
- Researcher in the fields of arrhythmic sudden death, heart failure and cardiomyopathy. Aswan Heart Centre, Aswan, Egypt under the supervision of Professor Sir Magdi yacoub.
- Egypt national leader in the INTER-CHF registry, an ongoing study investigating heart failure in middle and low economic countries. The research is steered by the Population Health Research Institute, Hamilton, Ontario, Canada. Principle investigators Hisham Dokainish and Salim Yusuf.
- Establishing clinical and invasive cardiac pacing and electrophysiology service, Aswan Heart Centre, Aswan, Egypt under the supervision of Professor Sir Magdi Yacoub.