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PROGNOSTIC VALUE OF THREE-DIMENSIONAL ELECTROANATOMIC VOLTAGE MAPPING IN PATIENTS WITH ARRHYTHMIAS OF RIGHT VENTRICULAR ORIGIN

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ABSTRACT

Endocardial voltage mapping (EVM) by CARTO system offers the potential to accurately identify the presence, location and extent of right ventricular (RV) low-voltage regions (i.e. electroanatomic scars) which may represent the substrate of life-threatening right ventricular tachyarrhythmias. This study prospectively evaluated the prognostic value of RV electroanatomic scars in a cohort of patients presenting clinically with arrhythmias of RV origin.

Methods

The study population comprised 109 consecutive patients (73 men and 36 women; mean age 36±14 years) with a left bundle branch block pattern ventricular arrhythmia, of which 21 with ventricular tachycardia (VT), 64 with non sustained VT, frequent and/or repetitive premature ventricular beats were detectable in 24 patients. All patients underwent detailed clinical evaluation and high density RV EVM by sampling multiregional RV bipolar electrograms (197±23 sampled points) to identify RV electroanatomic scars (defined as low-amplitude areas with bipolar electrogram <0,5 mV).

Results

Electroanatomic scars were found in 54 patients (49%), affecting 20,4±13,0% (range 2,6% to 49,8%) of the RV free wall. The presence of electroanatomic scar significantly correlated with a positive family history (P<0,001), late potentials on SAECG (P<0,001), and RV dilatation/dysfunction (P<0,001). During the follow-up, mean period of 49±13 months, 25 of 109 patients (23%) experienced malignant arrhythmic events such as sudden death in 2, cardiac arrest due to ventricular fibrillation in 4, appropriate ICD intervention in 7, and unstable VT leading to syncope in 12. Unexplained syncope (P<0,001) and electroanatomic scar (P<0,001) were significantly associated with the arrhythmic events. Among patients with an abnormal RV EVM, those who experienced arrhythmic events during follow-up had a significantly greater percentage of electroanatomic scar (27,4±10,5% versus 16,0±12,3%, p<0,001). After adjustment for age, family history, VT, and RV dilatation/dysfunction, unexplained syncope (OR=15,9, 95%CI=4,1-61,8; P<0,001) and RV electroanatomic scars (OR=9,28, 95% CI=2,0-42,7; P=0,004) remained independent predictors of malignant arrhythmic outcome.

Conclusions

Electroanatomic scars were found in approximately half of patients with significant arrhythmias of right ventricular origin. There was a significant correlation between electroanatomic scar extent and incidence of arrhythmic events during follow-up. Electroanatomic scar, unlike RV dilatation/dysfunction, was an independent predictor of malignant arrhythmic outcome.

RIASSUNTO

La mappa elettroanatomica di voltaggio con sistema CARTO permette di identificare e caratterizzare (presenza, sede ed estensione) aree di miocardio ventricolare caratterizzate da basso voltaggio elettrico, cosiddette "cicatrici elettroanatomiche", che rappresentano un possibile substrato per tachiaritmie ventricolari pericolose per la vita.
Questo studio si propone di valutare prospetticamente il valore prognostico della presenza di cicatrici elettroanatomiche in una popolazione di pazienti con aritmie ad origine dal ventricolo destro.

Metodi

La popolazione studiata era costituita da 109 pazienti (73 maschi e 36 femmine, età media 36±14 anni) giunti consecutivamente alla nostra osservazione per la comparsa di aritmie ventricolari con aspetto tipo blocco di branca sinistra, che includevano tachicardia ventricolare sostenuta in 21, tachicardia ventricolare non sostenuta in 64 e battiti ventricolari prematuri frequenti e/o ripetitivi in 24 pazienti.
Tutti i pazienti sono stati sottoposti ad una dettagliata valutazione clinica e alla mappa elettroanatomica di voltaggio del ventricolo destro eseguita registrando elettrogrammi bipolari multiregionali (197±23 punti) allo scopo di identificare la presenza di cicatrici elettroanatomiche (definite come aree con voltaggio elettrico inferiore a 0,5 mV).

Risultati

La presenza di cicatrici elettroanatomiche è stata documentata in 54 pazienti (49%). L'estensione della cicatrice elettroanatomica, espressa come area percentuale di parete libera del ventricolo destro con voltaggio elettrico inferiore a 0,5mV, variava da 2,6% a 49,8% (media 20,4±13,0%). La presenza di cicatrice elettroanatomica risultava associata in maniera statisticamente significativa con storia familiare positiva (P<0,001), dimostrazione di potenziali tardivi al SAECG (P<0,001) e presenza di dilatazione/disfunzione del ventricolo destro (P<0,001). Durante un follow-up di 49±13 mesi, 25 pazienti (23%) hanno presentato eventi aritmici maligni, quali morte improvvisa (2 pazienti), arresto cardiaco da fibrillazione ventricolare (4 pazienti), intervento appropriato dell'ICD (7 pazienti) e sincope secondaria a tachicardia ventricolare (12 pazienti).

All’analisi univariata le uniche variabili cliniche-elettrofisiologiche predittive di eventi aritmici nel follow-up risultavano una storia positiva per sincope aritmica (P<0,001) e la presenza di cicatrice elettroanatomica (P<0,001). Nei pazienti con un mappa elettroanatomica di voltaggio anormale, la comparsa di eventi aritmici durante il follow-up si associava ad un’estensione della cicatrice elettroanatomica significativamente superiore (27,4±10,5% verso a 16,0±12,3%, P<0,001). All’analisi multivariata, la sincope inspiegata (OR=15,9, IC 95%=4,1-61,8; P<0,001) e la presenza di cicatrice elettroanatomica (OR=9,28, IC 95%=2,0-42,7; P=0,004) rimanevano predittori indipendenti di rischio aritmico, dopo correzione dei dati per età, storia familiare, presenza di tachicardia ventricolare e dilatazione/disfunzione del ventricolo destro.

Conclusioni

La presenza di cicatrici elettroanatomiche veniva documentata in circa metà dei pazienti con aritmie ad origine dal ventricolo destro.

I pazienti con cicatrice elettroanatomica presentavano più spesso storia familiare positiva, potenziali tardivi e dilatazione/disfunzione del ventricolo destro.

L’estensione della cicatrice elettroanatomica correlava con l’incidenza di eventi aritmici durante il follow-up. La presenza di cicatrice elettroanatomica, a differenza della dilatazione/disfunzione del ventricolo destro, costituiva un marker predittivo indipendente di rischio aritmico.

FIRST CHAPTER

Ventricular arrhythmias originating from the right ventricle

Ventricular arrhythmias: background

The definition of ventricular arrhythmias corresponds to ectopic activity beyond to His bifurcation: by definition there are not been included both arrhythmias originating from His bundle because it is considered as a part of atrio-ventricular junction both arrhythmias leading to accessory pathways even if involving ventricular myocardium[1].

Ventricular activation from ectopic site necessarily differs from normal because the electric signal, bypassing the common conduction pathways, determines an asynchronous ventricular contraction and a morphologic and duration changing of QRS.

Ventricular arrhythmias include, more frequently, premature ventricular beats (PVB), mono- and polymorphic ventricular tachycardia (VT), torsades de pointes, ventricular flutter (VFl) and ventricular fibrillation (VF).

The QRS morphology allows to accurately identify the origin of ventricular arrhythmias, i.e. a left bundle branch block (LBBB) morphology indicates a right ventricular origin, while a right bundle branch block (RBBB) morphology indicates an origin from the left ventricle (LV).

Nevertheless sometime, as in the presence of ischemic or dilated cardiomyopathies, left bundle branch block morphology, may correspond to left ventricular origin, particularly from the interventricular septum[1].

QRS axis also gives some useful information; i.e. ventricular arrhythmias with RBBB morphology and inferior axis may originate from base, right ventricular outflow tract (RVOT), superior end and of left interventricular septum or from left ventricular free wall. Inferior left QRS axis indicates an origin from the superior right ventricular free wall or from interventricular septum while superior axis shows an origin from septum, apex or apical-lateral regions [1].

Besides, other QRS aspects, reliable at surface ECG, can clarify ventricular arrhythmias genesis. For example, more rapid is first deflection of QRS, more probable is the origin from normal myocardium, while the slurring of the early electrical forces is associated with an origin from scar tissue or with epicardial origin [2]. It is important, therefore, underline that low voltages may indicate the presence of serious structural myocardial disease [2].

The mechanisms responsible of ventricular arrhythmias are divided into tree categories: reentry, abnormal automaticity and triggered activity [1].

A reentry mechanism is implicated overall in the genesis of ventricular tachycardias associated with the presence of ischemia or myocardial infarction; structural discontinuities that separate muscle bundles as a result of naturally occurring myocardial fiber orientation and anisotropic conduction as well as collagen matrices formed from the fibrosis after myocardial infarction, establish the basis for slowed conduction, fragmented electrograms and continuous

electrical activity that can lead to reentry. The activation of this mechanism is related to the following conditions:

- two or more regions with different conductive properties and refractory forming a closed circuit,
- a unidirectional block in a conduction pathway
- a slowing of the impulse travelling trough the alternative pathway.

In other words, the original impulse that travels down A (Fig. A), is blocked in its anterograde direction at site B (arrow followed by double bar), but continues slowly down C (serpentine arrow) to excite ventricular muscle. If the impulse continues to propagate trough A and elicits ventricular depolarization, a re-entrant ventricular extrasystole results. Continued reentry of this type would produce ventricular tachycardia.

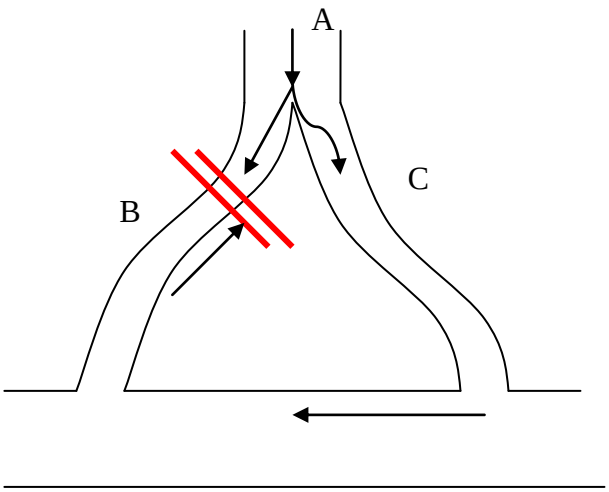


Figure A: Mechanism of reentry

The automaticity is usually a peculiarity of sinus node cells, atrioventricular node cells and bundle of His-Purkinje fibres (specialized myocardium). These cells with this characteristic, defined as pace maker cells, activate ordinary myocardium throughout electric membrane action potential: Na^+ ion inward current enhances the electric membrane potential reaching the threshold for activation of other cells and propagation of impulse.

Besides the principals pace maker cells, there are other ventricular cells, usually concealed, with the property of being dominant. The increasing of catecholamines, both endogenous both exogenous, electrolytic disorders (i.e. hyopkaliemia and hypercalcemia), hypoxia and ischemia,

mechanical effects as the ventricular stretch and some drugs as digoxin, may increase the automaticity (Fig. B) [102].

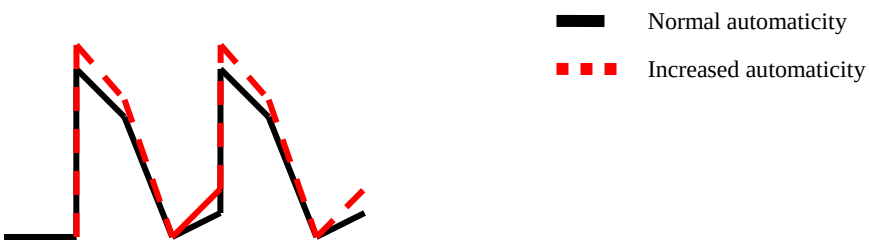


Figure B: Increased automaticity

Triggered activity is initiated by *after-depolarizations*, which are depolarizing oscillations in membrane voltage induced by one or more preceding action potentials. Thus, triggered activity is pacemaker activity that results consequent to a preceding impulse or series of impulses, without which electrical quiescence occurs. Usually, after-depolarizations are secondary to sarcoplasmatic reticular Ca^{2+} increase. Not all afterdepolarizations may reach threshold potential, but if they do, they can trigger another afterdepolarization and thus self-perpetuate [102].

Ventricular arrhythmias originating from right ventricle

Right ventricular arrhythmias are hyperkinetic arrhythmias with LBBB-like QRS morphology and are generally divided into categories: arrhythmias with idiopathic or organic origin.

Arrhythmogenic right ventricular cardiomyopathy is the most common structural substrate of right ventricular tachycardia (VT), followed by congenital heart diseases, sarcoidosis and myocarditis. Less common causes include dilated cardiomyopathy (DCM) and ischemic cardiomyopathy. In the context of structural right ventricular (RV) abnormalities, especially ARVC/D, VT may herald sudden arrhythmic death. On the other hand RV tachycardia is often due to idiopathic VT, mainly originating from the RVOT. Idiopathic RV tachycardia is a non-familial and benign condition that occurs in young individuals without structural heart disease (Fig. C).

Therefore identification of structural RV myocardial substrate is critical because it implies different prognosis and management strategies.

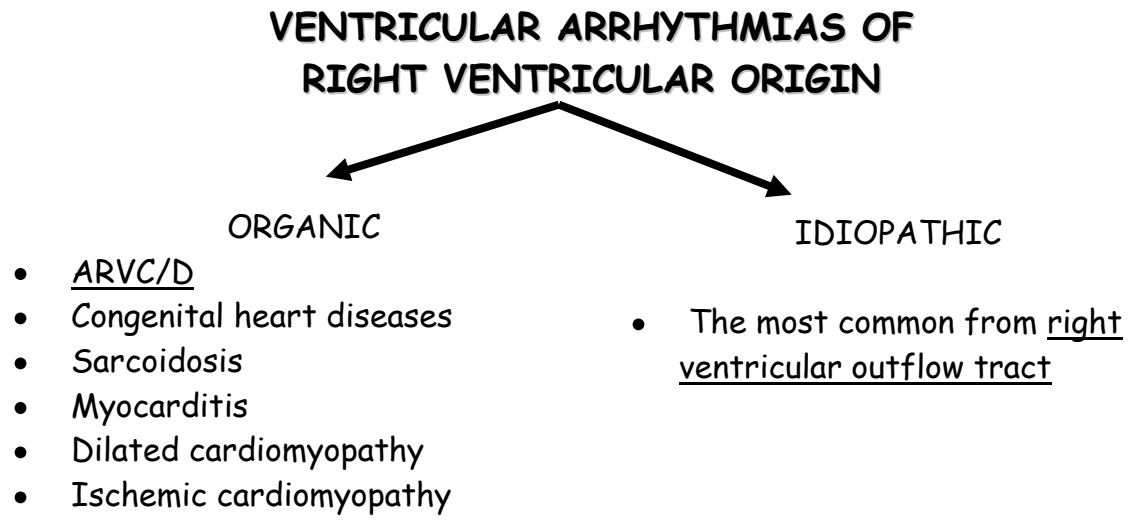


Figure C: The most common cause of right ventricular

Idiopathic ventricular tachycardia originating from right ventricle

Idiopathic RV tachycardia is a ventricular arrhythmia that occurs without structural heart disease, therefore it is considered as primarily electric disease [3] and it represents 10% of right ventricular arrhythmias. Some studies have identified as principle causes, the channelopathies (i.e. long QT syndrome, Brugada syndrome, catecholaminergic ventricular tachycardia) and some not well established diseases, but linked to Purkinje fibers disorders (i.e. fascicular tachycardia responsive to Verapamil and idiopathic ventricular fibrillation) [4].

Differential diagnosis may be difficult especially with ARVC/D at its early stage or in its minor variant, which are characterized by clinically subtle myocardial abnormalities without evidence of ventricular dilation/dysfunction.

Although approximately 90% arise from the right ventricular outflow tract (RVOT), the remainder are from the left. These two types of arrhythmias represent only one entity so called "arrhythmias of outflow tract" with a common embryologic origin [5,6].

The microscopic and ultra-structural findings of outflow tract differ to respect of the other atrial and ventricular myocardium, presenting cells with early embryologic phenotype with low proliferation rate, decreased propagation velocity of electric impulse and "primitive" contractile phenotype (with sarcoplasmatic reticular and sarcomeric structures poorly developed and with smooth muscle alpha-actin persistently expressed). This histological characteristic is probably linked to the pathogenesis of the arrhythmia [7].

The ventricular tachycardia originating from the right ventricular outflow tract has a left bundle branch block morphology with inferior axis, with positive QRS complex in DII, DIII and aVF and negative QRS complex in aVL (Figure 1).

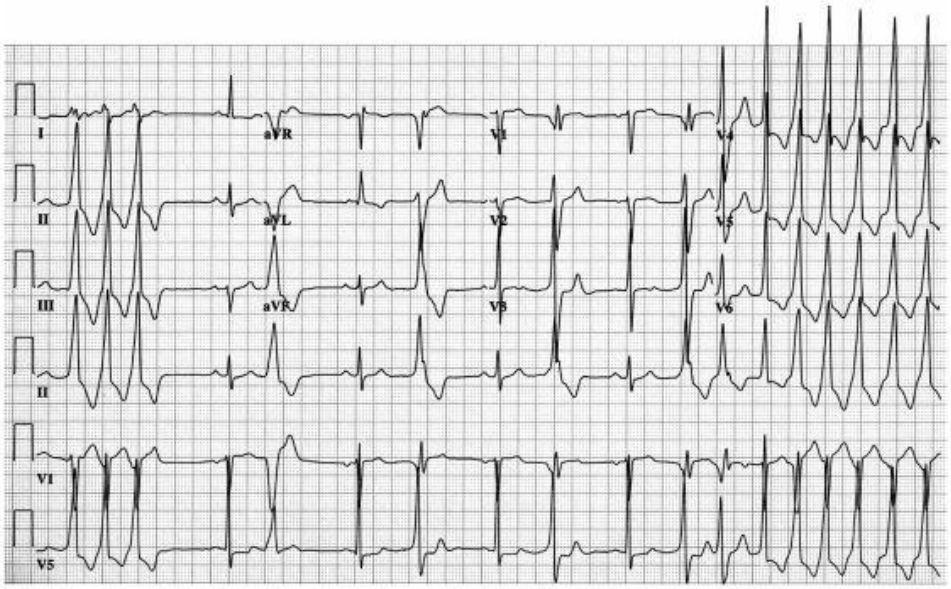


Figure 1 Monomorphic ripetitive ventricular tachycardia originating from the right ventricular outflow tract, with LBBB/inferior axis QRS morhology. From [103]: *Srivathsan K. et al. "Ventricular tachycardia in the absence of structural heart disease". Indian Pacing Electrophysiol J 2005; 5(2): 106-121.*

The frequency of this arrhythmias is estimated to be 2:1 in females versus males, and its first manifestation is usually from the second to the fifth life decade as palpitations, atypical chest pain, dizziness and syncope (10% of cases) [8].

Two clinical manifestations of this tachycardia have been described: non sustained, repetitive monomorphic ventricular tachycardia (RMVT) and sustained paroxysmal ventricular tachycardia (SPVT). The RMVT (whose example is showed in Fig.1) presents the following characterizes:

- it is more frequent
- it appears particularly at rest
- its duration is inferior than 30 seconds
- it is repetitive (sometimes incessant)
- it presents frequent premature ventricular beats
- usually it is asymptomatic and its diagnosis is accidental
- programmed ventricular stimulation doesn't reproduce it

while the SPVT:

- is linked to physical exercise and to stress
- has duration more than 30 seconds
- can alternate to prolonged intervals of sinusal rhythm
- presents some premature ventricular beats
- usually is inducible [1,4].

Pathogenesis

Idiopathic tachycardia, that originates from right ventricular outflow tract, responds to adenosine, beta-blockers, Ca^{2+} channel-blockers and vagal manoeuvres.

For this reason, this arrhythmia is probably linked to electrophysiological mechanism like the triggered activity due to the afterdepolarizations cyclic adenosine monophosfate (cAMP)-dependent [4]. Afterdepolarizations, which are depolarizing oscillations in membrane voltage, can occur before or after full repolarization of the fiber and are correctly termed *early afterdepolarizations* (EADs) when they arise from reduced level of membrane potential during phases 2 (type 1) and 3 (type 2) of the cardiac action potential or called *late or delayed afterdepolarizations* (DADs) when they occur after completion of repolarization (phase 4), generally at a more negative membrane potential than that from EADs arise. DADs most likely play a causative role in arrhythmogenesis; they are generally linked to an excessive Ca^{2+} accumulation in the sarcoplasmatic reticulum and

spontaneous sarcoplasmatic reticular Ca^{2+} release, secondary to a lot of conditions, i.e. catecholamines or digoxin influences. In patients with idiopathic tachycardia, beta-adrenergic stimulation can initiate signal system that profoundly alter the fluxes of calcium and other ions. Membrane G protein-coupled receptors are responsible of the signal transduction with the activation of a sarcolemmal enzyme, adenylyl cyclase that sets in motion a series of signals that terminate with activation of certain crucial proteins i.e. phosphokynase A (PKA). Phosphorylation by PKA increases entry of calcium ion through increased opening of the voltage-dependent L-type calcium channels into the cell acting as a trigger for the release of Ca^{2+} ions from sarcoplasmatic reticulum. The increased cytosolic Ca^{2+} levels promote membrane Na^{+}/Ca^{2+} exchange pumps, with a subsequent Na^{+} entry and membrane voltage increasing (Figure 2). With a different mechanism, i.e. ATP-ase Na^{+}/ K^{+} pump blocking, digoxin may increase intracellular calcium overload, which may be responsible of the genesis of arrhythmias [4].

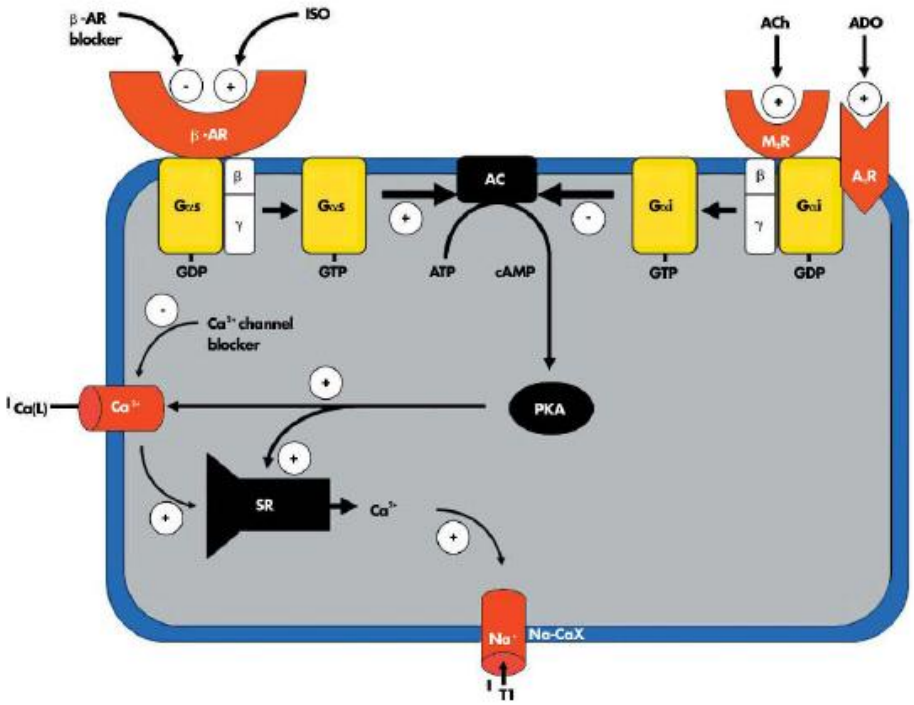


Figure 2 Triggered activity cAMP-linked, due to the presence of delayed afterdepolarizations. Beta-adrenergic receptor (βAR) stimulation on GDP/GTP exchange of stimulatory G protein (Gas), activates the adenylyl cyclase increasing cAMP and subsequently phosphokynase A (PKA). Thus, the consequence is an increase of entry of calcium ion through the long-lasting voltage-dependent channels (ICa(L)) into the cell and an increase of Ca^{2+} ions release from sarcoplasmatic reticulum (SR) extruding the calcium overload through the membrane Na^{+}/Ca^{2+} exchanger (Na-CaX). Adenosine (ADO), by binding to its specific receptor (A1R), acts via an inhibitory G protein (Gαi). The active Gai-GTP complex inhibits adenylyl cyclase with a consequent decrease of ICa (L) current and sarcoplasmatic reticular release, with attenuation of transient current ItI. Ach, acetylcholine; ISO, isoproterenol; M2R, muscarinic cholinergic receptor. From [4]: *Farzaneh-Far A et al. "Idiopathic ventricular outflow tract tachycardia". Heart 2005; 91: 136-138.*

Although it has been well studied the ionic mechanism of this arrhythmia, its causes are not well understood. Therefore it is clear that this tachycardia is a non-familial condition and occurs in absence of structural heart disease. Nevertheless Farzaneh-Far et al. [4] reported a case of atypical or adenosine insensitive idiopathic ventricular tachycardia from right ventricular outflow tract, in which it has been isolated a somatic point mutation in the inhibitory G protein (localized at GTP-binding domain) with increase of intracellular cAMP concentration in response to catecholaminergic stimulation. This mutation was characteristically present only in the myocardial site of origin of the arrhythmia while it was not identified at myocardial sites disparate from the site of origin consistent with a somatic origin of the tachycardia.

In ventricular myocardium delayed after-depolarizations mainly originate from M cells, localized at middle myocardium layer, which present intermediary characteristics among those of Purkinje fibres and those of the ordinary myocardium and are sensitive to adrenergic stimulation. The great prevalence of M cells on the right ventricular outflow could explain why the most common origin of arrhythmias is from this site [4].

The pathogenesis of this arrhythmia may clarify the results of electrophysiological study and of the therapy.

As previously described, adenosine can terminate this arrhythmia by blocking, through inhibitory G protein stimulation, the adenylyl cyclase and the subsequent cascade (Fig.2).

Adenosine action is specifically directed only to mechanisms cAMP-linked which, in turn, regulates Na^+ and Ca^{2+} currents, but doesn't influence the delayed after-depolarizations stimulated by digitalis, as well has no influence either on the discontinue arrhythmias generated by early after-depolarizations and it doesn't influence arrhythmias due to reentry or increased automaticity mechanisms [4].

Less specific is the action of beta-blockers and Ca^{2+} which are able to stop arrhythmias due to reentry or increased automaticity mechanisms. Thus, these drugs interrupt idiopathic tachycardia blocking respectively adrenergic stimulation and trans-membrane Ca^{2+} currents.

Finally, vagal manoeuvres, as carotid sinus massage or Valsalva manoeuvre, interrupt tachycardia activating the receptors inhibitory G protein-linked that is the same final target of adenosine [4].

Diagnosis

The diagnosis of idiopathic tachycardia is done by exclusion. The basal surface ECG of patients is usually normal. The arrhythmia occurs in 25%-50% in correspondence of physical activity, both during exercise, both during rest. Signal average ECG is negative for presence of post potentials [8]. Echocardiography usually appears normal; the most common abnormality is prolapse of mitral valve without regurgitation or myxomatous thickened leaflets [8]. A mild enlargement of left and/or right ventricles has been also found.

As previously described, there are two clinical entities responsible of arrhythmias originating from right out flow tract: idiopathic tachycardia and arrhythmogenic right ventricular cardiomyopathy/dysplasia. Because natural course and management of these arrhythmias are different, various strategies have been utilized.

Some authors have found at MRI mild structural anomalies of right ventricle, as parietal thinning, fatty infiltration, regional kinetic abnormalities in a great percentage of patients with idiopathic tachycardia (up to 70% for Markowitz et al [3]). Nevertheless these findings don't appear to be on arrhythmic substrate because different electrophysiological studies have not shown any correlation between the structural alterations and the site origin of arrhythmias [3].

On the base of the available knowledge, mild ventricular structural and functional abnormalities, shown in patients with idiopathic tachycardia from right outflow tract, may represent an early stage of ARVC or a consequence of recurrence tachycardias (it has been demonstrated that repetitive premature ventricular beats from right outflow tract can also determinate a *tachycardiomyopathy* appearance, completely reversible with ablation therapy [9]), or they may represent the result of a pathological process through a triggered-activity mechanism while fatty replacement or wall thinning may be represent an aspecific result.

Nevertheless many interpretative doubts remain, because of contradictory results of different studies and because similar structural abnormalities detected in healthy subjects [10].

Idiopathic tachycardia from outflow tract is reproducible by programmed ventricular stimulation. The reentry tachycardias was regarded as inducible by extra-stimuli, while those secondary to triggered activity were spontaneous and therefore not inducible [11].

It has been shown, instead, that also the tachycardias secondary to post-potential can be reproduced, in particular circumstances, by extra-stimuli, even if the most frequent mechanism of induction remains however a rapid "burst" [12]. The induction of the tachycardia is facilitated by the infusion of isoproterenol, atropine and aminophylline (all substances that, by direct or indirect way, increase the intracellular concentration of cAMP).

Management

The therapy of idiopathic tachycardia originating from right ventricular outflow tract is secondary to pathogenetic mechanism.

Acute management: carotid sinus massage or Valsalva manoeuvres are the first line approach while if they fail adenosine is the initial drug of choice followed by verapamil or lidocaine.

Long-term management: it is indicated only in the presence of pre-syncope or syncope or when recurrence tachycardia begin weakening.

The idiopathic tachycardia originating from outflow tract of the right ventricle responds to all the classes of antiarrhythmics with a success estimated around 25%-50%. The beta-blockers represent the first medication in term of quality. In alternative Ca^{2+}-antagonists are also suitable as antiarrhythmics of class 1A or of class 1C. The antiarrhythmics of class 3, as amiodarone and sotalol, have an effectiveness of 50%. Excellent results are obtained with ablation therapy, with a very low rate of relapse.

Prognosis

The prognosis of this arrhythmia is considered favourable, despite the frequent episodes of ventricular tachycardia, because of absence of cardiac structural pathology. Buxton et al. report an increased risk of sudden death in patients affected by ventricular tachycardia without cardiac structural disease, not recommending any therapy [12]. On the contrary, Corrado et al. indicates an increased sudden death risk, correlated with to a clinical overlap with precocious forms of arrhythmogenic dysplasia [10].

To note that the benign nature of the idiopathic tachycardia from outflow tract has been put in discussion because the right ventricle outflow tract can origin ectopic beats with short coupled intervals, able to switch on polymorphic tachycardia, and premature beats able to trigger ventricular fibrillation [13].

Arrhythmogenic right ventricular cardiomyopathy/dysplasia

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a genetically determined heart muscle disease that predominantly affects the right ventricle (RV), characterized pathologically by myocardial atrophy and fibro-fatty replacement of the right ventricular myocardium [14-16]. It is characterized clinically by right ventricular electrical instability leading to ventricular tachycardia (VT) or ventricular fibrillation (VF), which may precipitate sudden cardiac arrest mostly in young people and athletes [17-19]; a prospective study reports 20% of sudden death cases in young people less old than 35 years and 22% in young athletes [15].

The condition was originally supposed to be a developmental defect of the RV myocardium, leading to the original designation of "dysplasia" (so called for the first time by Frank et al.) [20]. This concept has evolved over the last 25 years into the current perspective of a genetically-determined "cardiomyopathy" to indicate an acquired myocardial alteration.

On the basis of its nature of progressive heart muscle disease of unknown aetiology, ARVC has been more appropriately included among the cardiomyopathies (as the hypertrophic, dilated and restrictive cardiomyopathies) in the recent classification proposed by the task force of the World Health Organization/International Society and Federation of Cardiology [21,22].

The prevalence of the disease has been estimated to vary from 1:2.000 to 1:5.000; the disease affects men more frequently than women, with an approximate ratio of 2,7:1[23].

A familial background has been demonstrated in 30-50% of ARVC/D cases. A familial history of ARVD/C is present in 30% to 50% of cases. The most common pattern of inheritance is autosomal-dominant with incomplete penetrance and variable expression, although an autosomal-recessive pattern has also been reported in cardio-cutaneous phenotypes as Naxos and Carvajal diseases. The ARVC/D.

Genes involved in disease pathogenesis encode desmosomal proteins [24] which provide continuous cell-to-cell binding, i.e. intercalated discs (Fig. 3A) (together with gap junction or nexus and adherens junction) and offer mechanical attachment between cells (a schema of desmosomal structure is shown in Fig. 3B).

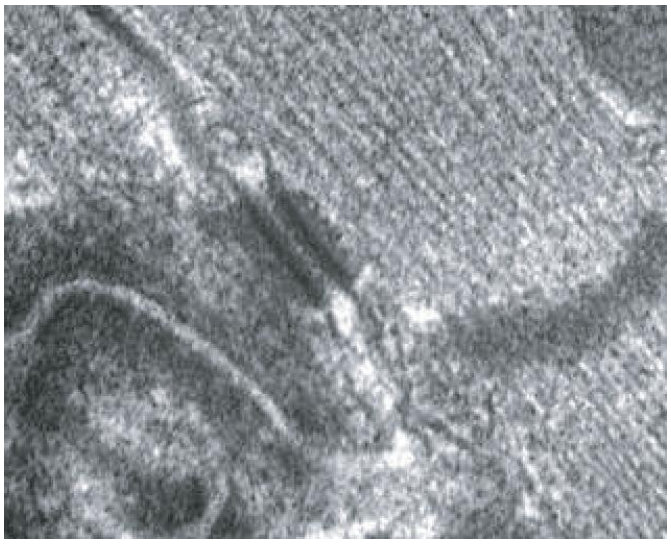


Figure 3A: Intercellular mechanical junction (desmosome) of the cardiomyocyte. Transmission electron microscopy of cardiomyocyte desmosome (boxed area, ×80 000).
From [104]: *Basso C., Corrado D., Marcus F.I., Nava A., Thiene G.: Arrhythmogenic right ventricular cardiomyopathy. Lancet 2009; 373: 1289–1300*

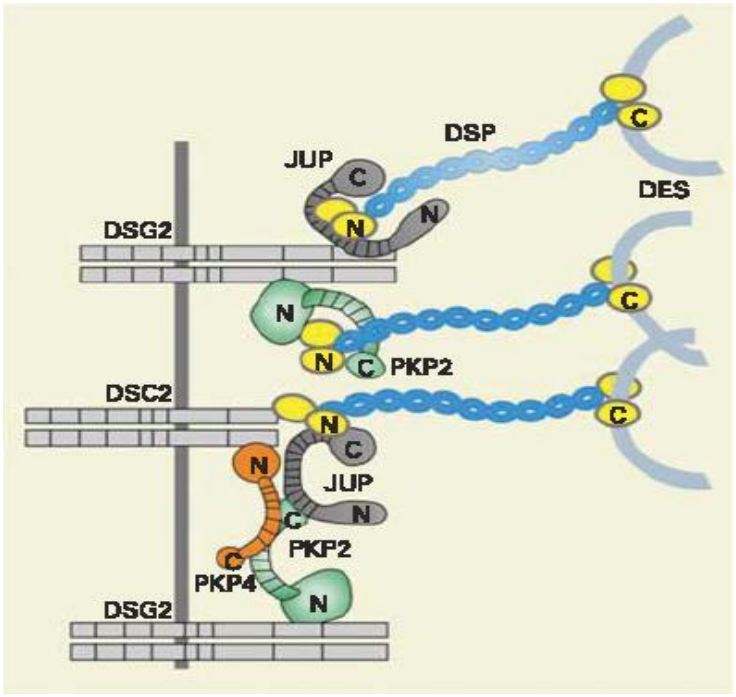


Figure 3B Schematic representation of desmosomal structure. There are three major groups of desmosomal proteins: (1) transmembrane proteins (desmosomal cadherins) including desmocollins (DSC) and desmogleins (DSG); (2) desmoplakin (DSP), a plakin family protein that binds directly to intermediate filaments—that is, desmin (DES) in the heart; and (3) linker proteins (armadillo family proteins) including plakoglobin (JUP) and plakophilins (PKP) which mediate interactions between the desmosomal cadherin tails and desmoplakin. From [105]: *Bevilacqua M., Migliore F., Basso C., Thiene G. and Corrado D.: Arrhythmogenic right ventricular cardiomyopathy/dysplasia. Brugada R., Brugada J., Brugada P. Eds.: Springer 2010-Chapter 13, 163-173.*

How the mutations of desmosomal protein genes cause disease remains to be elucidated. It has been hypothesised that the lack of the protein or the incorporation of mutant protein into cardiac desmosomes may provoke detachment of myocites at the intercalated discs, particularly under

condition of mechanical stress (like that occurring during competitive sports activity). As a consequence, there is a progressive cardiac cells degeneration and death with subsequent repair by fibrofatty replacement [25]. This could explain a greater involvement of the right ventricle with thinner parietal thickness and of the thin left ventricular lateral-posterior wall. This can also clarify why the disease affects men more frequently overall during intensive physical activity.

The availability of molecular testing for mutation screening of disease genes allows to identify genetically affected individuals in nearly 40% of cases [26-31].

The first chromosomal locus (14q23-q24) was published in 1994 after clinical evaluation of a large Venetian family. Subsequently, linkage analysis provided evidence for genetic heterogeneity with sequential discovery of several ARVC/D loci on chromosome 1 (1q42-q43), chromosome 2 (2q32.1-q32.2), chromosome 3 (3p23), chromosome 6 (6p24), chromosome 10 (10p12-p14 and 10q22), and chromosome 14 (14q12-q22). Other families analyzed with markers linked to these loci failed to show linkage, indicating further genetic heterogeneity. An autosomal recessive variant of ARVC/D (so-called Naxos disease) in which there is a cosegregation of cardiac (ARVC/D), skin (palmoplantar keratosis) and hair (woolly hair) abnormalities has been mapped on chromosome 17 (locus 17q21). The first disease-causing gene, the JUP gene, was identified by McKoy et. in patients with Naxos disease. The gene encodes desmosomal protein plakoglobin, which is the greater constituent of cell adhesion junction. Its discovery suggested that ARVC/D is a cell-to-cell junction disease and stimulated the research for other related genes. Subsequently mutations in desmosomal protein genes have been shown also to cause the more common (nonsyndromic) autosomal dominant form of the disease. Desmoplakin was the first defective gene to be associated with autosomal dominant ARVC/D by Rampazzo et al. Thus, Gerull et al. identified 25 different mutations in the gene encoding plakophilin-2 (PKP2) in 32 out of 120 ARVC/D probands (27%). More recently, mutations of the gene encoding for desmoglein-2 and desmocollin-2 have been involved in the disease pathogenesis.

The most common mutations actually identified are shown in Table 1.

Table 1 Dominant autosomal genetical variants of arrhythmogenic right ventricular cardiomyopathy actually identified, alterated chromosomal locus, involved gene and its function. From [112]: *D. Corrado, C.Basso, G. Thiene "Arrhythmogenic right ventricular cardiomyopathy: an update". Heart 2009; 95:766–773.*

Variant (pattern of inherence)	**Locus**	**Gene**	**Name and Function**
ARVC 1 (AD)	14q24.3	TGFβ3	**Transforming growth factor-β3:** Cytokin stimulating fibrosis and involved in intercellular adhesions metabolism
ARVC 2 (AD)	1q42-q43	RYR2	**Cardiac ryanodine receptor:** Calcium channel responsible for calcium release from the sarcoplasmatic reticulum
ARVC 3 (AD)	14q12-q22	Unknown	
ARVC 4 (AD)	2q32.1-q32.2	Unknown	
ARVC 5 (AD)	3p23	TMEM 43	**Transmembrane 43:** Membrane protein adipogenic grow factor receptor-linked
ARVC 6 (AD)	10p12-p14	Unknown	
ARVC 7 (AD)	10q22.3	Unknown	
Naxos disease (AR)	17q21	JUP	**Plakoglobin:** Desmosomal protein
ARVC 8 (AD)	6p24	DSP	**Desmoplakin:** Desmosomal protein
ARVC 9 (AD)	12p11.2	PKP2	**Plakophilin-2:** Desmosomal protein
ARVC 10 (AD)	18q12.1	DSG2	**Desmoglein-2:** Desmosomal protein
ARVC 11 (AD)	18q12.1	DSC2	**Desmocollin-2:**Desmosomal protein
ARVC 12 (AD)	17q21	JUP	**Plakoglobin:** Desmosomal protein

AD: autosomal dominant; AR: autosomal recessive

Autosomal dominant ARVC/D has been linked to other genes unrelated to cell adhesion complex, such as the gene encoding for cardiac ryanodine receptor (*RyR2*), which is responsible for calcium release from the sarcoplasmic reticulum, and the transforming growth factor-β3 gene (*TGFβ3*), which regulates the production of extracellular matrix components and modulates expression of genes encoding desmosomal proteins.

ARVC 2 linked to RYR2 mutation [32] is usually considered as a distinct variant of arrhythmogenic right ventricular cardiomyopathy because its clinical presentation is like

catecholaminergic polymorphic ventricular tachycardia, which affects poorly the myocardial morphology, wihout the typical fibro-fatty replacement.

The replacement of the right ventricular myocardium by fibrofatty tissue has been related to three basic mechanisms: 1) apoptosis or programmed cell death; 2) inflammatory heart disease with a spectrum of clinical presentations ranging from acute myocarditis to fibrous healing, which in severe forms may involve both right and left ventricles and may lead to congestive heart failure mimicking dilated cardiomyopathy; 3) myocardial dystrophy which might reflect a genetically determined atrophy. In this setting, a genetic propensity to infectious and/or immune reaction may explain the occurrence of myocarditis [16,33].

The most striking pathologic feature of ARVC is the diffuse or segmental loss of the myocardium of the right ventricular free wall and its replacement by fibrofatty tissue; it is frequently transmural with a wave front progression of the pathological process from the subepicardium to the endocardium (Fig. 4).

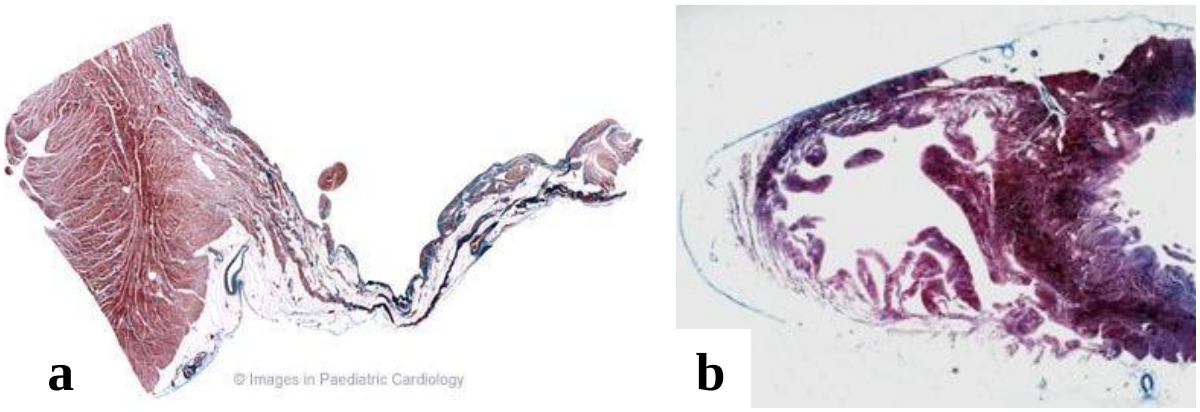


Figure 4 a. Histological feature of posterior aneurysmal in patient affected by arrhythmogenic right ventricular cardiomyopathy: note the wall thinning linked to myocardial atrophy and the transmural fibro-fatty replacement. From [105]: *Turrini P., Basso C., Daliento L* **RV** *L., Thiene G. "Is ar* **LV** *genic right ventricular cardiomyopathy a pediatric problem too?" Images Paediatr Cardiol 2001; 6: 18-37*; **b.** Transversal cut of heart affected by ARVC/D showing the interventricular septum (on the left) not involved by the disease and the right ventricular free wall (on the right) with nearly transmural fibrofatty replacement. From [107]: *Thiene G., Corrado D., Basso C. " Arrhythmogenic right ventricular cardiomyopathy/dysplasia". Orphanet Journal of Rare Diseases 2007; 2: 45-60.* RV, right ventricle; LV, left ventricle.

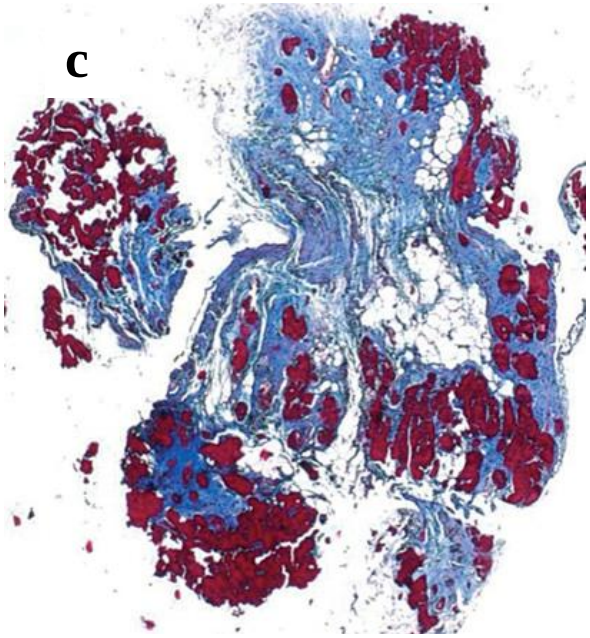


Figure 4 c. Endomyocardial biopsy sample with extensive myocardial atrophy and fibro-fatty replacement (trichrome; x6). From [104]: *Basso C., Corrado D., Marcus F.I., Nava A., Thiene G.: Arrhythmogenic right ventricular cardiomyopathy. Lancet 2009; 373: 1289–1300*

Although this disease was originally considered a disease involving exclusively the right ventricle, despite morphologic left ventricular features appear normal, the study *in vitro* of the hearts before with MRI (magnetic resonance imaging) and after with histology, has shown a left ventricular involvement (usually confined to subepycardium of lateral-poterior wall) in more than 50% of cases [14,17].

Because there is difficulty in differentiating ARVC from other causes of fatty infiltration of the right ventricular myocardium, as the normal amount of subepicardial adipose tissue reflecting the physiologic process of progressive involution of the right ventricle in healthy subjects (particularly in the elderly), or as the pathologic conditions including chronic consummation of alcohol and inherited myopathies such as Duschenne/Backer muscular dystrophy and many cardiomyopathies, histomorphometric criteria have been advanced in order to enhance the specificity of histopathologic diagnosis of ARVC at endomyocardial biopsy. A percentage of fat > 22% and of fibrous tissue > 31% with amounts of myocites < 59% was considered a clear cut diagnostic border between ARVC and other conditions, with a sensitivity respectively of 50%, 50% and 80% [34].

The disease is characteristically progressive with four phases: 1) **concealed phase**, clinically asymptomatic, with minor structural abnormalities confined to the so called triangle of dysplasia (inferior wall, apex and out flow tract); in this phase cardiac arrest may be the first and last manifestation of the disease. 2) **Overt electrical disorder**, with palpitations and syncope. The most typical clinical presentation is characterized by symptomatic right ventricular arrhythmias and progressive involving of right ventricle valuable with imaging techniques. 3) **RV failure.** The

progressive loss of the RV myocardium may impair the mechanical function of the RV and account for severe pump failure. 4) **Biventricular failure** mimicking dilated cardiomyopathy.

Although natural history indicates a strong correlation between symptoms and morphological and functional abnormalities of right ventricle, sometimes the disease appears in asymptomatic patients with advanced involvement [35]. Therefore the classification in 4 phases is often not respected because biventricular failure or the only left ventricular involvement may be present in the first phase of the disease [36,37].

Thus, actually is seems more correct to identify three clinical features of the disease: 1) classic ARVC with dominant involvement of right ventricle; 2) ALVC (arrhythmogenic left ventricular cardiomyopathy) with left ventricle more involved than right ventricle; 3) biventricular feature with the same involvement of both ventricles.

Diagnosis

The diagnostic criteria of arrhythmogenic right ventricular cardiomyopathy are often revised.

For example a modification of Task Force Criteria defined in 1994 [38] for the diagnosis of ARVC/D has been proposed in case of family members for early detection of the disease [39] because with the original criteria there was often difficulty to identify other cases in the family's proband because of incomplete penetrance and the polymorphism of the disease.

Therefore new tools for improving diagnostic accuracy have been introduced in recent years, as contrast or three-dimensional echocardiography, MRI with gadolinium late enhancement and three dimensional electroanatomic mapping and new electrocardiographic parameters are been individuated in the last 15 years.

At the end, the original criteria proposed a subjective morpho-functional and histological studies of ventricles; thus it was necessary to introduce quantitative criteria to compare patients with healthy population.

The new criteria, as the original ones in 1994, distinguish into major and minor criteria taking into consideration the different specificity of structural, histological, electrocardiographic, arrhythmic and familiarity findings.

Bottom there are reported a comparison between different criteria proposed in Tables 2-4.

Table 2 Task Force Criteria of 1994 for ARVC diagnosis. ECG, electrocardiogram; SAECG, Signal Averaged Electrocardiogram. From [38]: *Mc Kenna W.J. 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 and Federation of Cardiology". Br Heart J 1994; 71: 215-218.*

Major Criterions	***Minor Criterions***
GLOBAL and /or REGIONAL DYSFUNCTION AND STRUCTURAL ALTERATIONS	
- Severe dilatation and reduction of RV ejection fraction with no or mild LV impairment. * -Localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulging) at the so called tringle of dysplasia - Severe segmental dilatation of RV	- Mild global RV dilatation or ejection fraction reduction with normal LV. * - Mild segmental dilatation of RV. - Regional RV hypokinesia.
** This criterion allows to differentiate ARVC from dilated cardiomyopathy. Note that when these criterions were proposed, ARVC was considered as a disease exclusively of right ventricle.*	
TISSUE CHARACTERISTICS OF WALL	
- Fibrofatty replacement of myocardium on endomyocardial biopsy.	
ECG REPOALARITAZION ABNORMALITIES	
	-Inverted T waves in right precordial leads (V2 and V3) in people aged >12 years * and in absence of right bundle branch block.
** T wave inversion in right precordial leads in people < 12 years old can considered as normal variant while it is rarely present after.*	
ECG DEPOLARITATION/CONDUCTION ABNORMALITIES	
-Epsilon waves or localized prolongation (.110 ms) of QRS complex in right precordial leads (V1–V3).	- Late potentials on signal-averaged ECG.

ARRYTHMIAS	
	- Left bundle branch block–type ventricular tachycardia (sustained or nonsustained) documented by ECG or Holter monitoring or exercise testing. -Frequent ventricular extrasystoles (>1000/24 h by Holter monitoring).
FAMILY HISTORY	
- Familial disease confirmed at necropsy or surgery.	- Family history of premature sudden death (<35 years) due to suspected ARVD/C. - Family history (clinical diagnosis based on present criteria).

Table 3 Proposed modification of Task Force criteria for the diagnosis of familial ARVC/D. SAECG, Signal Averaged Electrocardiogram. From [39]: *Hamid M.S. et al. "Prospective evaluation of relatives for familial arrhythmogenic right ventricular cardiomyopathy/dysplasia reveals a need to broaden diagnostic criteria". J Am Coll Cardiol 2002; 40: 1445-1450.*

THE FOLLOWING CONDITIONS ARE NECESSARY
- ARVC/D in First-Degree Relative Plus One of the Following:
• **ECG**: T-wave inversion in right precordial leads (V2 and V3) • **SAECG**: Late potentials seen on signal-averaged ECG • **Arrhythmia:** - LBBB type VT on ECG, Holter monitoring or during exercise testing - Extrasystoles >200 over a 24-h period* • **Structural or functional abnormality of the RV:** - Mild global RV dilatation and/or EF reduction with normal LV - Mild segmental dilatation of the RV - Regional RV hypokinesia

Table 4 Revised Task Force criteria. ECG, electrocardiogram; SAECG, Signal Averaged Electrocardiogram. From [108]: *Marcus F.I., McKenna W.J., Sherril D. "Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria". Circulation published on line Feb 19, 2010.*

MAJOR CRITERIA	**MINOR CRITERIA**
GLOBAL and /or REGIONAL DYSFUNCTION AND STRUCTURAL ALTERATIONS	
By **bidimensional echocardiography** - Regional akynesis, diskynesis or aneurysm of right ventricle And one of the following: - Outflow tract diameter of right ventricle at parasternal long-axis view ≥32 mm; corrected for body size ≥19 mm/m^2 - Outflow tract diameter of right ventricle at parasternal short-axis view: ≥36 mm; corrected for body size: ≥21 mm/m^2 - Fractional area change ≤33%	By **bidimensional echocardiography** - Regional akynesis, diskynesis or aneurysm of right ventricle And one of the following: - Outflow tract diameter of right ventricle at parasternal long-axis view: 29-31 mm; corrected for body size: 16-18 mm/m^2 - Outflow tract diameter of right ventricle at parasternal short-axis view: 32-35 mm; corrected for body size: 18-20 mm/m^2 - Fractional area change ≤40%
By **Cardiac Magnetic Resonance** - Regional akynesis/dyskinesis or dyssynchronous RV contraction And one of the following: - Right ventricular end diastolic volume (corrected for body size) ≥110 ml/mq in male and ≥100 ml/m^2 in female OR - Ejection fraction of right ventricle ≤40%	By **Cardiac Magnetic Resonance** - Regional akynesis/dyskinesis or dyssynchronous contraction of right ventricle And one of the following: - Right ventricular end diastolic volume (corrected for body size) ≥100 ml/mq in male and ≥90 ml/m^2 in female OR - Ejection fraction of right ventricle ≤45%

By **right ventricular angiography:** - Regional akynesis, diskynesis or aneurysm of right ventricle	
TISSUE CHARACTERISTICS OF WALL	
- By morphometric analysis, residual myocites <60% (or < 50% if estimated), with fibrous replacement of right ventricular free wall myocardium in at least one sample with or without fatty replacement of tissue	- At morphometric analysis, residual myocites <60-75% (or 50 to 65% if estimated), with fibrous replacement of right ventricular free wall myocardium in at least one sample with or without fatty replacement of tissue
ECG REPOALARITAZION ABNORMALITIES	
- T wave inversion in right precordial leads (V1, V2 and V3) or beyond, in individuals >14 years old, (in the absence of right bundle branch block with QRS ≥120msec)	- T wave inversion in right precordial leads (V1 and V2), in individuals >14 years old, (without right bundle branch block with QRS ≥120msec) or in V4, V5 or V6 - T wave inversion in V1, V2, V3 and V4), in individuals >14 years old, in the presence of right bundle branch block
ECG REPOALARITAZION ABNORMALITIES	
- Epsilon wave (reproducible low amplitude signals between end of QRS complex to onset of the T wave) in right precordial leads (V1 to V3)	- Late potentials by signal average ECG in at least one of 3 parameters (filtered QRS duration: ≥114msec, duration of terminal QRS <40μV: ≥38msec, root mean square of terminal 40msec: ≤20μV), in the absence of a QRS complex duration of ≥110msec on the standard ECG - Terminal activation duration of QRS ≥55msec, measured to the end of the QRS complex, including R prime, in V1 or V2

	or V3 leads, in the absence of complete right bundle branch block
ARRHYTHMIAS	
- Non sustained or sustained ventricular tachycardia of left bundle branch morphology with superior axis (negative or indeterminate QRS in D2, D3 and aVF leads, and positive in aVL)	- Non sustained or sustained ventricular tachycardia of right ventricular outflow configuration, left bundle branch block with inferior axis (positive QRS complex in D2, D3 and aVF leads, and negative QRS in aVL) or of unknown axis. - Greater than 500 premature ventricular beats/day by Holter monitoring
FAMILY HISTORY	
- ARVC/D diagnosis confirmed in a first degree relative who meets current Task Force criteria - ARVC/D diagnosis confirmed pathologically at autopsy or surgery in a first degree relative - Identification of a pathogenic mutation ** categorized as associated with ARVC/D in the patient under evaluation.	- History of ARVC/D in a first degree relative in whom it is not possible or practical to determine if the family member meets current Task Force criteria - Premature sudden death (before 35 years) due to suspected ARVC/D in a first degree relative
** A pathogenic mutation is a DNA alteration in a gene associated with ARVC/D that is expected to alter the encoded protein, is unobserved or very rare in large, non ARVC/D control population and has been shown to cause abnormal function of the protein, or is strongly expected to, or demonstrated linkage to the disease in a conclusive pedigree.	

On the basis of the first classification [38], diagnosis of ARVD/C was fulfilled in the presence of 2 major criteria, or 1 major plus 2 minor criteria, or 4 minor criteria from different groups while for the revised Task Force, definitive diagnosis is reached when two major criteria or 4 minor criteria are present; the diagnosis is borderline in the presence of 1 major plus 2 minor criteria, or 3 minor criteria. Finally diagnosis is suspected in the presence of 1 major criteria and 2 minor criteria.

The most common techniques and the principle peculiar findings are reported in figure 5.

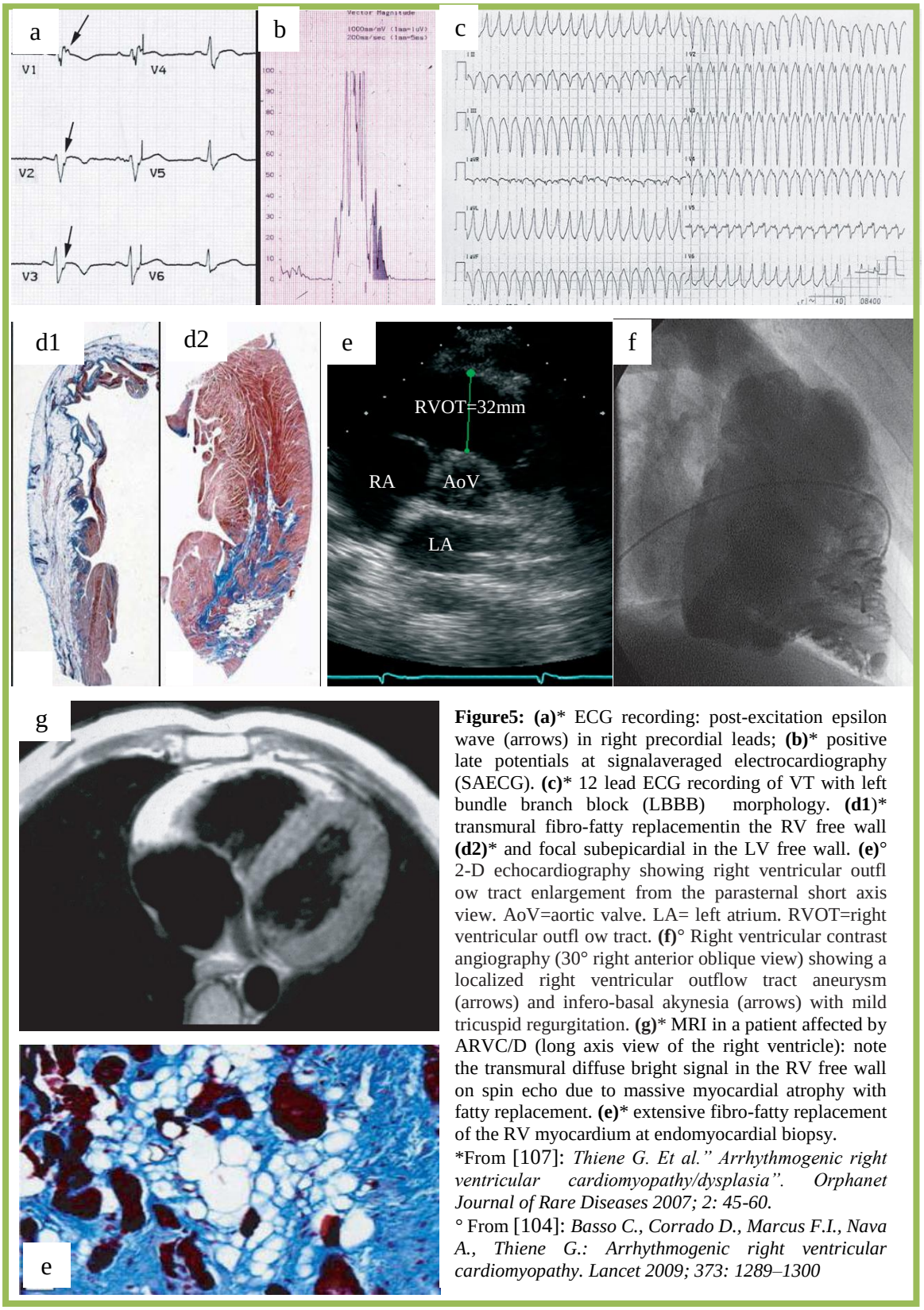


Figure5: (a)* ECG recording: post-excitation epsilon wave (arrows) in right precordial leads; **(b)*** positive late potentials at signalaveraged electrocardiography (SAECG). **(c)*** 12 lead ECG recording of VT with left bundle branch block (LBBB) morphology. **(d1)*** transmural fibro-fatty replacementin the RV free wall **(d2)*** and focal subepicardial in the LV free wall. **(e)°** 2-D echocardiography showing right ventricular outfl ow tract enlargement from the parasternal short axis view. AoV=aortic valve. LA= left atrium. RVOT=right ventricular outfl ow tract. **(f)°** Right ventricular contrast angiography (30° right anterior oblique view) showing a localized right ventricular outflow tract aneurysm (arrows) and infero-basal akynesia (arrows) with mild tricuspid regurgitation. **(g)*** MRI in a patient affected by ARVC/D (long axis view of the right ventricle): note the transmural diffuse bright signal in the RV free wall on spin echo due to massive myocardial atrophy with fatty replacement. **(e)*** extensive fibro-fatty replacement of the RV myocardium at endomyocardial biopsy.

*From [107]: *Thiene G. Et al." Arrhythmogenic right ventricular cardiomyopathy/dysplasia". Orphanet Journal of Rare Diseases 2007; 2: 45-60.*

° From [104]: *Basso C., Corrado D., Marcus F.I., Nava A., Thiene G.: Arrhythmogenic right ventricular cardiomyopathy. Lancet 2009; 373: 1289–1300*

Arrhythmogenesis

The most common clinical manifestations of ARVC consists of ventricular arrhythmias with left bundle branch block (LBBB) morphology.

Almost three mechanism may be involved in the arrhythmogenesis.
Macroreentry, mainly in the really advanced phases of the disease, is considered the most probable mechanism when patchy normal myocardium mixted to fibrofatty replacement, electrically inactive.

Recently it has been proposed a physiopathologic model that could explain the appearance of sudden life threatening arrhythmias in mild symptomatic or asymptomatic subject. As described for the right ventricular outflow idiopathic ventricular tachycardia pathogenesis, the electric activity, triggered by delayed after cAMP-linked depolarizations, seem to be involved in some forms of ARVC/D as in the ARVC2 type.

It is well known that this electric activity may be induced from the adrenergic stimulation. It has been shown that in cardiomyocites of patients affected by ARVC, there is an excessive synaptic concentration of catecholamines with relative down-regulation of the post-synaptic receptors. This excess of noradrenaline could be secondary to the increase of the pre-synaptic release of neuro-transmitter or to a reuptake deficit [40]. Remembering that the adrenergic stimulation begins the events cascade for the genesis of delayed after depolarisations, we can understand why the physical exercise is a factor of risk for sudden death in the initial phases of ARVC.

The third mechanism has been hypothesized after the demonstration that the mechanical defect of the desmosomes alters also function of the gap junctions (responsible of the electric coupling of the cardiomyocites) with a consequent negative remodelling as number and dimensions reduction of gap junctions, reliable by the electronic microscopy [41]. Thus, the altered syncizial function and the consequent conduction heterogeneity may contribute to the arrhythmogenesis.

Finally, the observation that, in one not negligible percentage of cases, the conduction tissue is also affected by fibro-adipose replacement has brought to propose that at least a part of the sudden deaths could be secondary to anomalies and/or arrhythmias originating from the same conduction tissue [42]. On surface ECG, in the context of right ventricular abnormalities, the depolarization dispersion, caused by the delay of impulse propagation, can appear as a QRS prolongation in right precordial leads rather than in left precordial leads.

The ventricular tachycardias ARVC/D linked as the idiopathic ventricular tachycardias, prevalently originate from outflow tract of the right ventricle. As previously described for idiopathic tachycardia, the outflow tract myocardium presents a peculiar structure that could partially justify arrhythmogenesis [7].

In conclusion, the arrhythmogenic mechanisms involved in ARVC/D, can be divided into two groups. The first one, primarily of cellular type and particularly linked to the post-potentials secondary to calcium and or catecholamine disorders, is responsible of the onset of arrhythmias especially in young patients with early stage disease and a great sudden death risk. The second one, scar related, is responsible for the onset of ventricular tachycardias in patient with disease of old date [43].

The disorders of electrical intracellular conduction, secondary to pathological involvement of gap junctions and of conduction tissue, create an electrical anysometry which represent an arrhytmogenic substrate.

Arrhythmic risk stratification

An open challenge is still represented by the patient risk stratification [44]. Furthermore, ARVC is a progressive disease and the patient's risk of sudden death may increase with time. The main objective of management strategy is to prevent arrhythmic sudden death. However, there are no prospective and controlled studies assessing clinical markers which can predict the occurrence of life threatening ventricular arrhythmias. All identified or suspected patients are at risk of sudden death even in the absence of symptoms or ventricular arrhythmias. The most challenging clinical dilemma is not whether to treat patients who already experienced malignant ventricular arrhythmias (secondary prevention), but to consider prophylactic treatment in
patients with no or only minor symptoms in whom the disease has been diagnosed during family screening or by chance (primary prevention).

It is still controversial the prognostic role of the invasive and not invasive investigations; in example, electrophysiologic study maintains a role primarily for diagnostic purposes and also to assess efficacy of AAD therapy in patients with VT [45], but was of limited value in identifying patients at risk of lethal ventricular arrhythmias [43].

Actually the risk profile which emerges from retrospective analysis of clinical and pathologic series, including fatal cases, is characterised by history of either cardiac arrest or ventricular tachycardia with hemodynamic compromised, syncope younger age, extensive right

ventricular disease with ejection fraction reduction and left ventricular involvement and family history of premature sudden death (< 35 years) [44].

Therapy management

The therapeutic strategies (summarized in Fig. 6) are divided into 2 groups, patients with low or high risk.

High risk for sudden death is defined by the presence of one of the following:

- positive family history for sudden death,
- younger age (less than 35 years),
- clinical positive history for syncope
- prior cardiac arrest,
- severe right ventricular dysfunction,
- left ventricular involvement,
- ventricular tachycardia/fibrillation hemodynamically compromised,
- QRS dispersion ≥40msec and
- epsilon wave on surface ECG

Patients presenting one or more of these characteristics are the best candidates for ICD implantation because there is evidence that ICD therapy, in this subgroup of patients, can effectively terminate malignant ventricular tachyarrhythmias in patients with ARVC/D leading to an improvement in long-term prognosis.

In contrast, in subgroup of patients with low risk, antiarrhythmic drugs (AAD) and catheter ablation seem to be a reasonable first-line therapy. Although a good acute success rate has been reported with catheter ablation, VT recurrences are common (up to 60% of the cases) and may lead to sudden arrhythmic death [69].

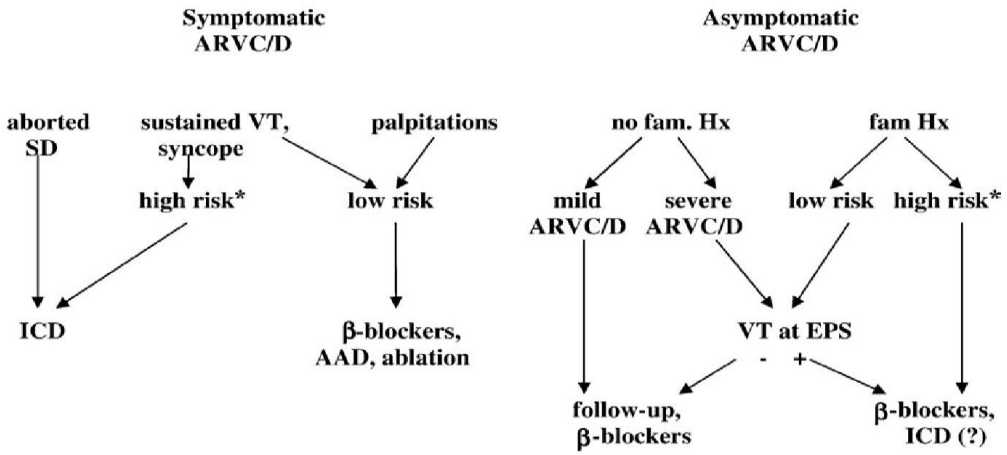


Figure 6 Algorithm for the antiarrhythmic management of ARVC/D. SD, sudden death; VT, ventricular tachycardia; AAD, antiarrhythmic drugs; ICD, implantable cardioverter-defibrillator; EPS, electrophysiological study; RV, right ventricle; LV, left ventricle. From [44]: *Buja G., Mark Estes N.A. III, Wichter T., Corrado D., Marcus F., Thiene G. "Arrhythmogenic right ventricular cardiomyopathy/dysplasia: risk stratification and therapy". Prog Cardiovasc Dis 2008; 50: 282-293.*

Cardiac sarcoidosis

Sarcoidosis is an inflammatory multisystem disease of unknown cause, characterized by predominant involvement of the lungs, liver, skin, and eyes.

It generally affects young individuals less aged than 40 years, with mild prevalence of females. No difference has been found about the geographical distribution and race, although in black Americans the disease presents more serious forms.

The histological peculiarity is represented by noncaseating epithelioid cell granulomas, in the absence of organisms or particles, in one or more organs (Fig. 7).

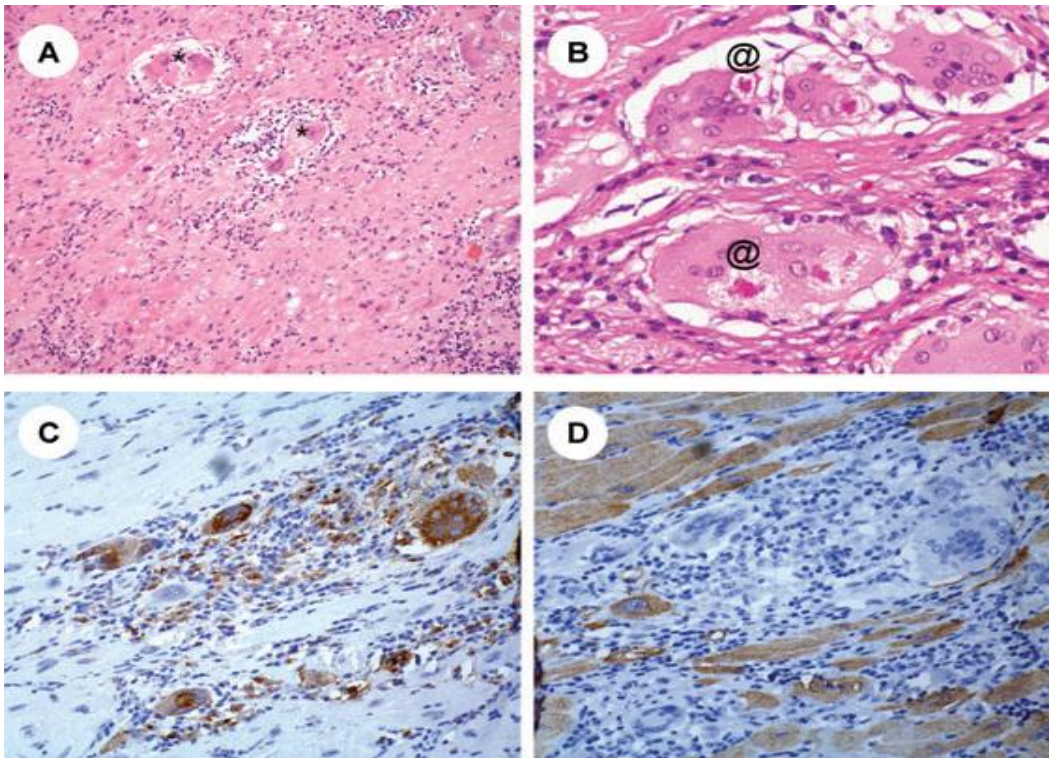


Figure 7 Biopsy specimens demonstrate, i*n the more fibrotic areas, some epithelioid cell granulomas were present (A, asterisk), with giant cells and asteroid bodies (@, B). Representative example of infiltrates of predominantly T lymphocytes (not shown) and also numerous giant cells (staining brown with the CD68 antibody, C), with cardiomyocytes damage (cardiomyocytes stain brown with the desmin antibody, D). Note that the giant cells are negative in the desmin staining and positive in theCD68 staining, proving the true histiocytic nature of these cells.From* [109]: *Ladyjanskaia G.A., Basso C., Hobbelink M.G.G. Kirkens H., Lahpor J.R., Cramer M.J. Thiene G., Hauer R.N.W., v Oosterhout M.F.M.: Sarcoid MyocarditisWith Ventricular Tachycardia Mimicking ARVD/C. J Cardiovasc Electrophysiol, Vol. 21, pp. 94-98, January 2010.*

The clinical presentation varies greatly, because every single organ can be affected by the disease. The most common involved localizations are more frequently in the lungs (90% of cases), in the limph nodes (hilar adenopathy in 90% of cases, peripheral lymph nodes in 30% of cases), the skin (25%) and in the uvea (25%). Although the cardiac involvement clinically appears alone in only 5% of cases, it represents an important cause of death, the second after respiratory failure and the first cause of death in the young patients.

The cardiac involvement has been reported with incidence ranging from 20% in postmortem studies in the United States to approximately 60% in Japan [46]. Nevertheless cardiac symptoms appear only in 5% of cases and consistent in ventricular dysfunction and arrhythmic disturbances as palpitations, syncope and sudden death.

Apparently Cotter in 1939 was the first to present the extensive changes in the myocardium caused by these nodes found at autopsy which resembled tubercles but differed from tuberculosis [47].

Iannuzzi et al. have reported the presence at autopsy of cardiac granulomas in 25% of patients affected by sarcoidosis [48].

Autopsy studies showed that the most common localization is the left ventricular free wall and less frequently the septum, generally affecting the conduction system [48]. Corrado et al. reported a RV free wall involvement in up to 40% of cases. The granulomatous infiltration leads to clinical LV or biventricular dilatation/dysfunction, conduction disease with bundle branch block patterns and AV block, and ventricular arrhythmias ranging from isolated premature ventricular beats to ventricular tachycardia, either sustained or non-sustained, and ventricular fibrillation leading to sudden death.

The arrhythmogenesis is probably linked to reentry mechanism for the presence of fibrosis.

The arrhythmic clinical features are often characterized by sudden onset of arrhythmias in apparently healthy individuals in whom only echocardiography and cardiac magnetic resonance can indicate ventricular morpho-functional abnormalities such as thinning, aneurysms and abnormal wall motion [49-51].

It has been demonstrated that cardiac sarcoidosis may account for the ARVC/D phenotype in an unexpectedly high proportion of cases [46]. ARVC and sarcoidosis do not differ with respect to most clinical variables such as age, symptoms, ECG abnormalities, late potentials, and arrhythmias. Thus, every patients with ARVC/D, particularly those with evidence of biventricular involvement, should undergo further diagnostic tests including, MRI and tree-dimensional electroanatomic voltage mapping to exlude the presence of sarcoidotic granulomas. Nevertheless only endomyocardial biopsy with an qualitative and quantitative analysis of samples, can give a

certain diagnosis [34], but EMB has a low diagnostic yield (less than 20%) because cardiac involvement tends to be patchy, and granulomas are more likely to be located in the left ventricle and basal ventricular septum than in the right ventricle, where endomyocardial biopsies are usually performed [48]. Nevertheless as Corrado et al. [46] suggest, the diagnostic accuracy and safety of EMB may be increased by targeting sampling through cardiac imaging-guided EMB.

Management therapy

Since sudden death can represent the first expression of this disease, electrophysiological study can be recommended in patients with arrhythmic disorders and suspicious of cardiac sarcoidosis.

The available evidence indicates that the indications for antiarrhythmic drugs, catheter ablation, and implantable cardioverter defibrillator are the same as for those with other cardiomyopathies at risk of life-threatening ventricular arrhythmias. In patients in whom cardiac sarcoidosis has progressed to severe ventricular systolic dysfunction, the treatment consists of current therapy for heart failure. In case of refractory congestive heart failure, patients may become candidates for cardiac transplantation [46,48].

Myocarditis

Myocarditis (or inflammatory cardiomyopathy) is classified between acquired cardiomyopathies [22].

It is an inflammatory process, acute or chronic, due to a various aetiologies including infections (particularly viral, but also bacterial, fungal and protozoal agents), toxins or medications (cocaine, etanol, lithium, fluorouracyle), secondary to hypersensitivity to drugs, myocarditis with giant cell [22,52,53].

The extreme diversity of clinical manifestations has made the true incidence of myocarditis difficult to determine [52]. Clinical presentations of the disease range from nonspecific systemic symptoms flu like (fever, myalgias, palpitations, or exertional dyspnea and chest pain mimicking an acute myocardial infarction) to fulminant hemodynamic collapse and sudden death [52,53]. Furthermore the diagnosis is often identified when myocarditis develops a dilated cardiomyopathy [53].

Normally histological evaluation of biopsies according to the Dallas criteria with demonstration of inflammatory infiltrate with or without necrosis under light microscopy gives a certain diagnosis of myocarditis. The presence of inflammatory infiltrate and myocyte necrosis leading to fibrosis, can determine the onset of reentry arrhythmias [22].

It is interesting to note that myocarditis mimicks arrhythmogenic right ventricular cardiomyopathy [54] and sometimes patients with ARVC are not distinguishable on the basis of clinical features, presence, and severity of structural and functional right ventricular abnormalities. Pieroni et al. [54] showed in their study that 3-dimensional electroanatomic mapping EAM findings sometimes don't differ between two disease, probably related to the persistence of myocardial inflammation rather than to scar tissue. In fact, myocardial inflammatory infiltrates associated with myocyte necrosis and replacement fibrosis, may lead to functional and structural changes of RV myocardium resembling those produced by fibrofatty replacement, and representing the substrate of the abnormal voltage map and ventricular arrhythmias.

This evaluation, together with the well note limitations of endomyocardial biopsy (considered however as the gold standard), suggests the necessity to perform EMB on the information base gotten from other instrumental investigations [46,54,85].

Dilated cardiomyopathy

Dilated cardiomyopathy, that is a mixed cardiomyopathy (genetics in the 20-35% of the cases and acquired in the other cases) [22], is characterized, unlike the conditions previously described, by predominant left ventricular involvement, leading to severe enlargement and progressive systolic dysfunction. The ventricular arrhythmias are frequent and there is an increased risk of sudden death for ventricular tachycardia or fibrillation [55,56]. Even if originating from the left ventricle, often the arrhythmias present left bundle branch block morphology, probably because they originate from the left portion of interventricular septum instead than from the free wall of the left ventricle [1].

Different mechanisms can explain the onset of arrhythmias in this disease. It has been shown a conduction disturbance of the impulse in epicardial layer, especially during programmed stimulation, that suggests the existence of a reentry mechanism [56,57]. Besides, the irregular distribution, in ventricular myocardium, of fibrosis could alter the impulse conduction. The

triggered activity, secondary to early or delayed delayed afterdepolarizations, can also determine the onset of arrhythmias in this cardiomyopathy.

Pogwizd et al. [58] have shown that the ectopic premature beats or the sustained ventricular tachycardias, spontaneous or induced by programmed stimulation, appear as a consequence of focal mechanisms (mainly localized at subendocardium layer), probably not involving macro-reentry. These results are opposite to the results of ischemic cardiomyopathy, in which mechanisms of reentry are recognized in at least the 50% of cases [59], suggesting that dilated cardiomyopathy is characterized by a greater percentage of focal mechanisms than of macro-reentry.

Even if this focal activity originates mainly from subendocardium, it has been shown an onset of ventricular tachycardia also from epicardium or from mean layer myocardium, suggesting an origin not necessarily only from Purkinje fibers, but also from M cells [58].

Pogwizd et to al. have shown that the focal origin of arrhythmias corresponds to lost muscular bundles in the context of fibrous tissue. Wilders et al. [60] have brought instead that the anysotropy facilitates the appearance of focal electric activity.

Congenital heart diseases

The incidence of ventricular tachycardia after surgical correction of congenital cardiomyopathies is relatively high, i.e. near 4-8% of the cases [61,62]. Usually the arrhythmias onset appears after 7-20 years from the correction and can represent a cause of sudden death in 1%-5% of these patients [63-65].

Ventricular tachycardia is most frequently after repair of the tetralogy of Fallot [63,66], but also the correction of the inter-ventricular defects, of the pulmonary vein congenital stenosis and of the great vessels transposition, presents a greater risk of serious ventricular arrhythmias and of sudden death.

The residual scar tissue, secondary to the surgical correction, represents the substrate for multiple circuits of reentry, but other mechanisms are also involved, because in 30% of patients with a documented ventricular tachycardia, the clinical arrhythmia is not inducible by programmed ventricular stimulation. Danefield et al. suggest a correlation between the arrhythmias and pulmonary hypertension and right ventricular hypertrophy found in some of these patients [67].

Unfortunately, the endocavitary mapping is not so easy in these patients because of the altered anatomical configuration secondary to the surgical correction [65]. Nevertheless, even if with these limitations, in corrected Fallot tetralogy it has been identified some circuits of reentry in right ventricular outflow tract [68]. The presence of reentry mechanisms is also supported by the inducibility of the tachycardia with programmed ventricular stimulation and because of the correspondence between the areas identified by endocavitary mapping from which arrhythmias are originating and the area of the surgical correction [65].

In patients affected by ventricular tachycardia hemodynamically well tolerated, the trans-catheter ablation seems to be possible while it is unadvisable in a long-term antiarrhythmic drug therapy in this subpopulation of patients, generally very young [65].

Differential diagnosis of right ventricular arrhythmias

Among the ventricular tachycardias with LBBB morphology, they have to be considered two principal entities: the ventricular pre-excitation syndrome and the supraventricular tachycardia with left aberration.

Ventricular pre-excitation syndrome

The premature activation is caused by muscular connections composed of working myocardial fibers that exist outside the specialized conducting tissue and connect the atrium and ventricle while bypassing atrio-ventricular (AV) nodal conduction delay [72].

From the point of connection between accessory pathway and ventricular myocardium, the pre-excited impulse travel in the ventricle by way of muscular fiber to fiber. This type of propagation, however, conducts the impulse more slowly than ordinarily, so, even if the impulse excites prematurely the ventricles, the conduction travels more slowly; the QRS complex begins in advance than usually, corresponding to a fusion beat as a result of depolarization of the ventricle in part by wavefront travelling over the accessory pathway (represented by delta wave) and in part by the wavefront travelling over the normal AV node-His bundle route.

The accessory pathways, unlike the AV node, don’t present a decremental conduction (conduction in which the intensity of the impulse decreases progressively by heart rate increasing);

therefore, in presence of high frequency supraventricular rhythm, the impulse can be integrally transmitted to the non protected ventricles. This effect is enhanced if the refractory period of the normal route is decreased, as it happens with digitalis therapy or vagal stimulation.

The presence of atrioventricular accessory pathway can give rise to paroxysmal tachyarrhythmias with left bundle branch block morphology (when the accessory pathway is anteroseptal or right lateral) presenting quite the same characteristics of mentioned tachycardias.

Ventricular tachycardias, unlike tachycardia linked to pre-excitation, show some peculiar characteristics: QRS complex predominantly negative in V4-V6, QR complex in one or more leads from V2 to V6, more QRS complex than P waves (in the presence, during ventricular tachycardia, of AV dissociation). These criterions present a sensibility of 75% and a specificity of 100% [73].

Since the accessory pathway is constituted by ordinary myocardium, the muscular fibers respond to the pharmacological agents as the muscular fibers of the ventricular myocardium. Thus, antiarrhythmic drugs of class 1C blocking the sodium channels, can slow the impulse conduction through the accessory pathway [72].

Supraventricular tachycardia with left aberration

Making the ECG distinction between supraventricular tachycardia with aberration leading to a pre-existing bundle block and VT can be difficult at times since feature of both arrhythmias overlap and under certain circumstances a supraventricular tachycardia can mimic the criteria established for VT above mentioned.

The intraventricular conduction disorders appear when the refractoriness in a conduction system tract, especially in a bundle or in a fascicle, don't have the sufficient time to complete the recovery. The most common site of the conduction delay leading to a slower recovery is in the tract with a greatest refractoriness, i.e. the right bundle[1].

The premature supraventricular beats aberration is often observed also in physiological conditions. The tachycardia with wide QRS complexes can be originated by occurring of runs of these premature beats.

It is not difficult to recognize these premature supraventricular beats when the abnormal QRS complex is preceded by a premature P wave; besides, the absence of a compensatory pause helps to confirm the suspect of not ventricular origin.

Diagnosis of ventricular arrhythmias

The ventricular tachycardias present a large variety of clinical manifestations ranging from asymptomatic or perceived as palpitations, dizziness, chest pain or syncope. Finally, if this tachycardias are hemodynamically compromised , they could be life-threatening arrhythmias.

It has been previously mentioned to the utility of a simple investigation as the electrocardiogram for the identification and the classification of the ventricular tachycardias: it has been shown that it is possible to determine the site origin of the arrhythmia [1] and, according to some authors, also the probable anatomical substrate [2].

An another useful investigation with the purpose to clarify the characteristics of the tachycardia and to appraise its association with the patient activities and with the clinical features, is represented by the dynamic electrocardiographic Holter monitoring. The Holter ECG, that takes the name from its inventor, Doctor Norman J. Holter, consists in the continuous recording, for 24 hours or more, of the cardiac electric activity.

As for the classical electrocardiography, the ECG Holter records the signals from electrodes positioned on the chest. The electrodes, whose position and whose number are varying according to the model utilized (usually ranging from three to eight), are connected to a device, that receives and records the signals. The recording utilizes digital flash memories, the data are transferred on computer and the software helps the physician in the reading and interpretation of the layout. In this way it is possible to analyze the heart electric activity for an wide time slice.

The electrophysiological study is another important investigation for the evaluation of the ventricular tachycardias. This examination can present manifold applications: it studies the conduction of the electric impulse, allows to better characterize the arrhythmias and to individualize their site origin and the impulse travelling through the myocardium tissue. The inducibility of some arrhythmias allows to hypothesize the mechanism that originates the conduction disorders (the inducibility with extra-stimuli suggests the existence of reentry tachycardias [12] while the inducibility with rapid bursts suggests the existence of focal tachycardias [69]). On the other hand the inducibility consents to choose the best management therapy (drug therapy, trans-catheter ablation). Finally this study, when induces the arrhythmias, allows to evaluate the efficacy of the antiarrhythmic drugs.

The diagnostic role of this technique is unquestionable, while the opinions about its prognostic value are still discordant. While the predictive value of the tachycardia inducibility is recognized in the context of the ischemic cardiomyopathy [70], the ventricular programmed stimulation shows an imperfect prognostic value because of the appearance of fatal arrhythmias in

the other cardiomyopathies, particularly in the arrhythmogenic cardiomyopathy of the right ventricle [43], in the hypertrophic and dilated cardiomyopathies [71].

More recently the three-dimensional voltage mapping has been introduced with very good perspectives. This technique, which will be described in the next chapter, has permitted to get all the information provided by the traditional electrophysiological study and also to find a possible anatomical substrate of the tachycardias, i.e. the anatomical scars reentry mechanism linked. Finally this method makes the trans-catheter ablation procedures easier, because it allows to repetitively drive the catheter in a same point with precision and with least necessity to use the fluoroscopy.

The strategies management of the ventricular arrhythmias

The ventricular tachycardia and fibrillation are the most common causes of sudden death. In a study about patients presenting an out-of-hospital cardiac arrest, it has been observed that at the arrival of the emergency care unit there was a ventricular fibrillation in the 40% of cases and that asystolia or electro-mechanics dissociation were so much more frequent as more the intervention was delayed [74].

Although in some cases of sudden death it's not evident cardiac structural abnormalities, the patients affected by cardiomyopathies are exposed to a superior risk. Among the cardiomyopathies with an increased risk of ventricular arrhythmias and sudden death, the acute ischemia and the myocardium infarct have a prominent role, causing the 50% of the sudden death cases [75].

Recent evidences, found in patients carrying implantable defibrillator for a previous cardiac arrest due to ventricular fibrillation or tachycardia, show that the ventricular tachycardia is the most frequent form of arrhythmic recurrence [76]. Nevertheless the clinical variables able to predict the risk of arrhythmic recurrence are not clear. For instance some types of arrhythmia are predictive for the sudden death: i.e. the non sustained ventricular tachycardia (overall in the patients with left ventricle dysfunction) or frequent and repetitive premature ventricular beats with positive correlation between beats number and arrhythmic risks [77,78].

Among the instrumental investigations, the SAECG shows to be useful in the stratification of the arrhythmic risk and in the correlation with the presence of the ventricular tachycardia, spontaneous or induced, but the predictive positive value remains extremely low and the technique gets more sensible and specific only in patients with ventricular dysfunction.

While the non invasive investigations (SAECG, electrocardiogram Holter monitoring, echocardiogram) are often inadequate, the invasive ones, overall the electrophysiological study, are more accurate for the risk stratification [79].

About the management therapy of the arrhythmias, there are two main approaches: the antiarrhythmic drug therapy and the defibrillator implantation. The ICD therapy is appropriate for the patients with sudden death high risk (previous cardiac arrest, reduced ejection fraction, non sustained and sustained ventricular tachycardia hemodinamically compromised, inducibility of the ventricular tachycardia) and it seems more effective than the drug therapy with amiodarone.

Welch et al. [79] suggest to limit the use of the antiarrhythmic drug therapy to the patients with recurrent arrhythmias, in which the defibrillator interventions are frequent, because we have to remember that the antiarrhythmic drugs are themselves proarrhythmic and can be dangerous more than useful.

SECOND CHAPTER

The three-dimensional electroanatomic voltage mapping with CARTO system

Basic principles of the three-dimensional electroanatomic voltage mapping

The conventional electrophysiological mapping system records the local activation times (LATs), at different mapped spots, in comparison with a reference either on the surface electrocardiogram or a selected intracardiac signal. This technique presents a significant limitation because of the necessity to employ the fluoroscopy control to check the catheter position: in addition to the risks associated with the X-rays exposure, this system doesn't provide a complete information about the orientation and position of the catheter tip in a three-dimensional heart chamber. The exact location of the catheter tip is a precious information when repeated catheter navigation to a desired location is required during radio frequency ablation.

The CARTO system [80,81] uses low energy magnetic fields (from 5×10^{-6} T to 5×10^{-5} T) to locate the catheter tip. Under the examination table there are three magnetic coils creating magnetic fields around the patient's chest. Every coil produces a magnetic field that decays in rapport with the distance from the same coil [81].

The catheter utilized with the CARTO system contains a magnetic sensor, located near the distal electrode, that permits precise positioning of the catheter with a resolution power lower than 1 mm about the position in the three-dimensional space and lower than 1 degree about the orientation. The catheter design of CARTO system is not so different from that of a conventional mapping catheter, but it allows, unlike this one, to record unipolar and bipolar electrograms and it contains a thermocouple or thermistor for temperature monitoring, which is very useful during the ablation. Catheters are supplied with 4 or 8 mm tips and irrigated tips.

The sensor located on the catheter tips records the strength of the magnetic field produced by every coil under the examination table; the recorded strength is inversely proportional to the distance between the sensor and the coils. Converting the strength reported by the sensor in the measure of the distance is possible to locate precisely the point of the catheter, as illustrated in fig. 8 [81,82].

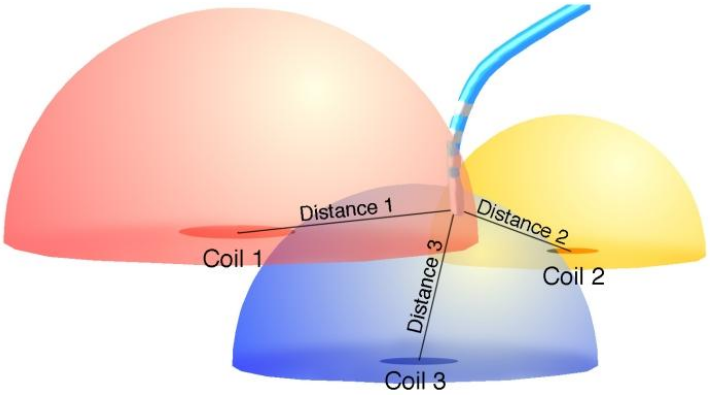


Figure 8 The catheter localization system. The three coils under the examination table create three magnetic fields, represented in this figure by the coloured hemisphere. The radius of each hemisphere (distance 1, distance 2, distance 3) reproduces the distance between the sensor on the catheter tip and the coil; this distance is in inverse relation to the power generated by each coil. The intersection of the three hemisphere determines the location of the catheter. From [82]: *Bhakta D., Miller J.M.: Principles of electroanatomic mapping. Indian Pacing Electrophysiol J 2008; 8(1): 32-50.*

The interferences provoked by the patient movements are eliminated through the input analysis by a location sensor placed on the back of the patient.

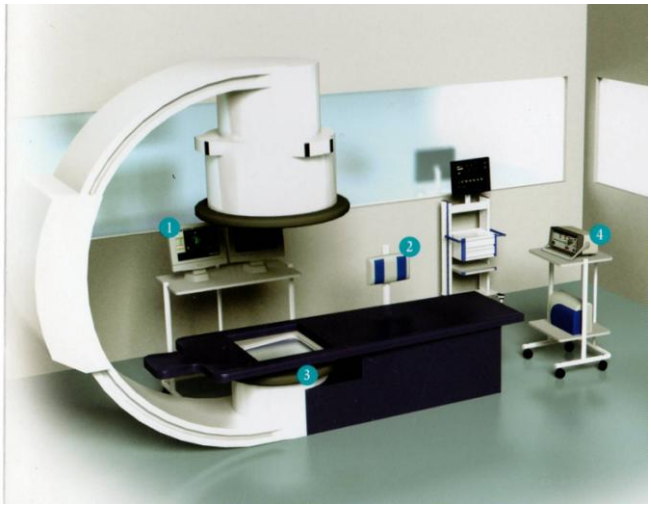


Figure 9 A model of electrophysiological laboratory with CARTO System. 1: flat screen monitor; 2: patient interface unit; 3: location pad; 4: stockert RF generator for the ablation therapy.

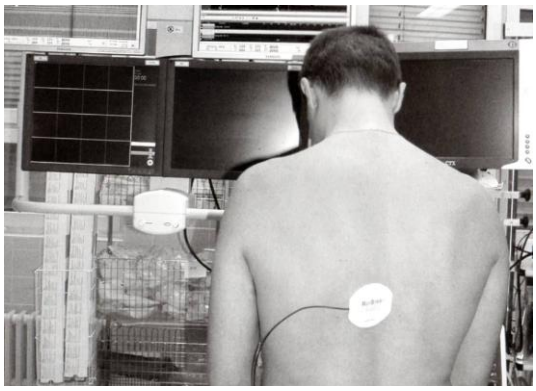


Figure 10 The patch placed on the back of the patient contains a sensor utilized to give a location reference useful to eliminate the interferences provoked by the patient movements. From [80]: *Kautzner J. et al. Electro-anatomical mapping. An illustrated guide to the use of the CARTO System. Remedica Publ, 2006, Chicago, London, pp. 1-26.*

The intracardiac mapping consists in the systematic acquisition of points through the contact of the catheter tip with the endocardium (or the epicardium); for each of these touching points the system records the exact spatial position and the local electrogram. The peculiarity of this technique is the combination, for each point, of the electric information with the exact anatomical position. Through the sequential acquisition of the points it's possible to create in real time a three-dimensional anatomical map; therefore the quality of the map is a reflection of number of points acquired. The anatomical reconstruction of the mapped cardiac structure is done in real time because the system allows an immediate editing of acquired data.

The achieved anatomical map can be visualized from each side and angle and it's possible to apply to it some electrophysiological data expressed through a colour-coding. Consequently it's possible to create: 1) the activation maps that provide the information about the sequence and the velocity of activation (Fig. 11); 2) the isochronous maps that depict with the same colour all the points which have an activation time within a specific range (Fig. 12); 3) the propagation maps that, after finishing the activation map, allow the visualization of the electrical activation (Fig. 13); 4) mesh maps in which the mapped structure appears as a fine transparent net, facilitating the visualization of the underlying points (i.e. useful to guide the ablation) (Fig. 14); and finally 5) voltage maps that permit the acquisition of the local electrocardiograms amplitudes (Fig. 15).

Figure 11 Activation map. This is the lateral view of a cardiac chamber. The map shows the early conduction near the asterisk indicated with orange colour, while the slow conduction zone is indicated with blue colour. *From* [80].

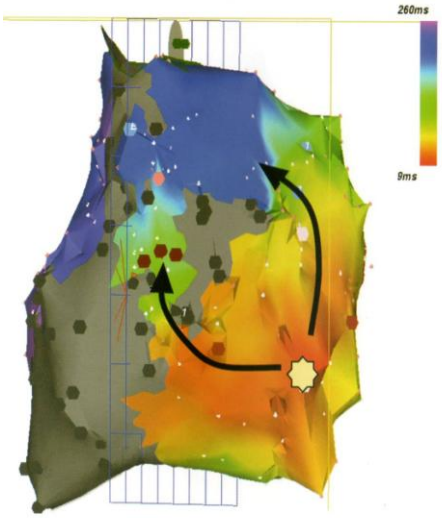


Figure 12 Isochronous map. This map depicts with the same colour all the points which have an activation time within a specific range. *From* [80].

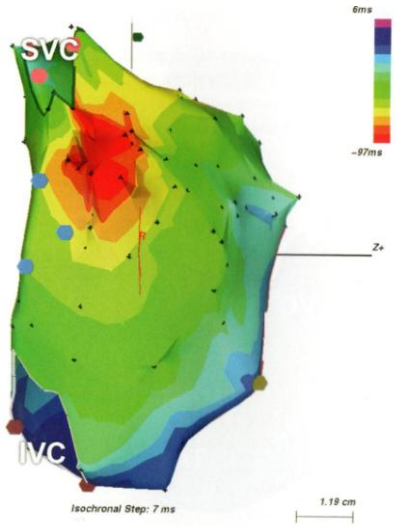


Figure 13 Propagation maps of the left ventricle (anteroposterior view) during focal ventricular tachycardia originating from the apex (red arrow). *From* [80].

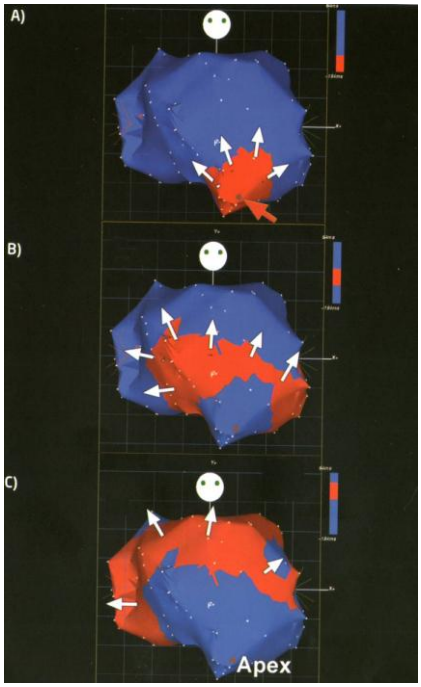
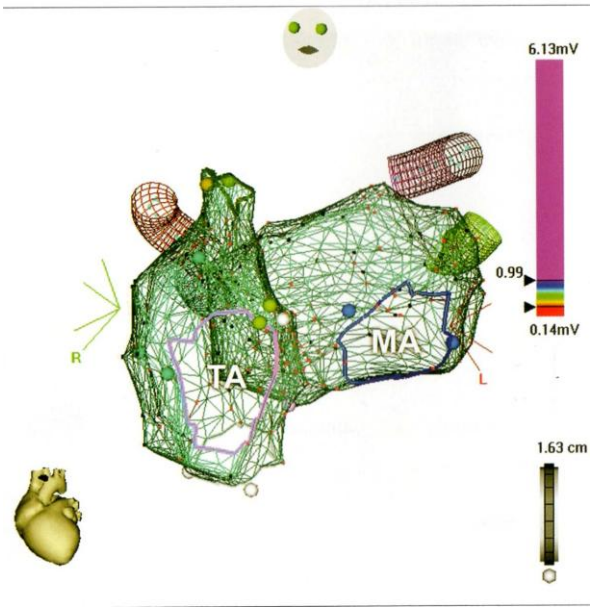


Figure 14 Mesh map of both atria (left anterior oblique view). *From* [80].



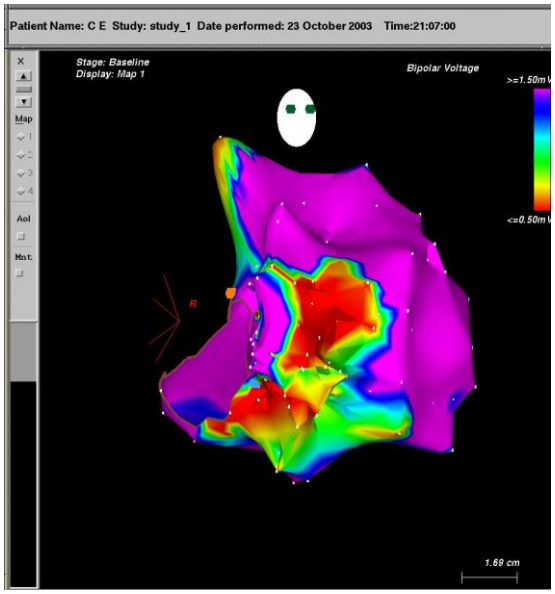


Figure 15: voltage map (right anterior oblique view of the right ventricle). Voltages are colour coded according to corresponding colour bars: purple represents signal amplitudes >1.5 mV (electroanatomic normal myocardium); red, <0.5 mV (electroanatomic scar tissue); and the range between purple and red, 0.5 to 1.5 mV (electroanatomic border zone).

With this technique it's possible to obtain a three-dimensional geometrical reconstruction of the shape and size of the specific cardiac structure from which its volume can be calculated and it's also possible, if necessary, to determine the dimensions and the form of specific anatomical structures, as for instance the tricuspid anulus or the coronary sinus.

We can also measure the distance between two acquired points, facilitating the design of the ablation lines and come back in the same point many times, with high operation reproducibility and minimal need for fluoroscopy. All the mapped points are recorded as black points on the three-dimensional map: in this way, using specific commands, it's possible to guide the catheter along ways already studied.

Limitations of the electroanatomic mapping

Despite the undoubted advantages, the electroanatomic mapping presents also a number of inherent limitations. This technique inevitably requires a long time because it needs a sequential point by point mapping. Furthermore the system is only able to map cardiac rhythms with constant cycle lengths. Thus, it's not possible to create a map of an unstable arrhythmia with varying cycle lengths.

Another limitation is that the system is as easier as the surface is more regular. In consequence the mapping of sharp ridges of tissues or the ostia of the veins, is very difficult.

Three-dimensional electroanatomic voltage mapping: the procedure

Location of the reference sensor

As previously explained, the patient movements can cause some interferences during the data collecting. To reduce to a minimum the effects of chest movements, we have to secure with a location sensor, placed in an adhesive reference patch, on the patient's back (around the seventh intercostal space paravertebrally).

The sensor position within the heart should be checked with fluoroscopic investigation before beginning of the procedure; it's also better to set the reference patch close to the chamber that is to be mapped, because there's a certain pre-defined range which the the catheter tip can be localized.

The patient should be placed approximately 10 cm above the catheterization table, so that his chest is in alignment with the electromagnetic field produced from below the table [80].

Choice of the reference signal

This phase is crucial. The selection of the reference signal is dependent on what is the chamber of interest. For example, if we want to map the atria, it's better to choice as reference a stable intra-atrial signal (i.e. a signal coming from the coronary sinus) or the recording coming from the right atrium.

Instead, if we want to map the ventricular chambers, it's advisable to use the QRS complex recorded on a traditional electrocardiographic lead: the preferred leads are those with marked deflections of the R or S waves, i.e. the precordial leads, or those with the P or T waves very clear [79].

Definition of the window of interest and of the fill threshold

Defining the window of interest is fundamental in the set up because it determines the time frame of the cardiac cycle during which the acquisition of the mapping points will occur [80]. Generally the window of interest is centred around the reference signal, such that the limits of the window respectively precede and follow it.

Usually the window of interest should match the tachycardia cycle length, even if it varies depending on the origin of tachycardia (atrial or ventricular tachycardia). Overall, in case of ventricular tachycardia, as explained in our study, the window of interest should slightly precede the onset of the QRS complex on the surface electrocardiogram to acquire the mapping of both focal and reentry ventricular arrhythmias. However, in case of reentrant tachycardias, the window of interest should cover almost the entire cycle length of the ventricular tachycardia.

The software creates a continuous surface map of the chamber depending on the base of mapped points: as greater it's the number of points as greater it will be the image definition [80]. The fill threshold is the function that determines the level of interpolation and so the level of image definition; usually the fill threshold has to be equal to 15 unities to obtain detailed images. When we plan higher values, the system formulates an interpolation of the activation times among the mapped points and it fills the empty spaces, so that the image results anatomically less precise.

Maintaining endocardial contact between the catheter and the surface

To obtain an image with high quality definition, which we can analyze quantitatively and qualitatively, it's very important to maintain the contact between the catheter and the surface of the endocardium. This aspect is really essential for the creation of voltage maps because an inadequate contact can result in inaccurate or false maps.

Some expedients can reduce the cases of inadequate contact. First of all we have always to check by fluoroscopy that the catheter movements are synchronous with the cardiac contraction and the catheter position is within the cardiac contour.

The contact between the ablation catheter and the endocardium can be verified by the appearance of a small protrusion of the catheter tip icon on the surface of the electroanatomic map. It's possible to verify the adequate contact of the catheter also considering the characteristics of the recordings of electrograms: in case of good contact they will present high frequency or an increase in impedance.

The electroanatomic mapping of the right ventricle

The 7F Navi-Star catheter, which consisted of a 4-mm distal tip electrode and a 2-mm ring electrode with an interelectrode distance of 1 mm, is introduced into the RV under fluoroscopic guidance by femoral vein access (with Seldinger technique).

Generally the exam begins with the delimitation of the outflow tract, acquiring many points in circumferential way from the pulmonary valve. The electrocatheter is withdrawed and bended at the level of the intermediary septal area until to the right ventricular apex; then rotating the catheter in counterclockwise way and bending it further, it's possible to acquire the points on the free wall. The circumference of the tricuspid can be mapped surrounding it with the catheter.

However, the right ventricle is the most difficult chamber to map with this type of technique, especially when the RV dilatation makes hard the access to its different regions.

The electroanatomic voltage mapping

After the data collection, it's possible to apply to the anatomical reconstruction the electrophysiological information, i.e. measuring the amplitude of the electrograms recorded point by point: we create in this way a voltage map.

We use a colour-coding to define the ranges of voltage values: for the ventricular chambers red colour represents voltages lower than 0,5mV, purple colour the values higher than 1,5mV, while the range between red and purple colours represents the intermediary values between 0,5 mV and 1,5 mV.

Thus, red colour identifying the low voltage areas show the so called electroanatomic scars while purple colour show the electroanatomical normal tissue (Fig. 16).

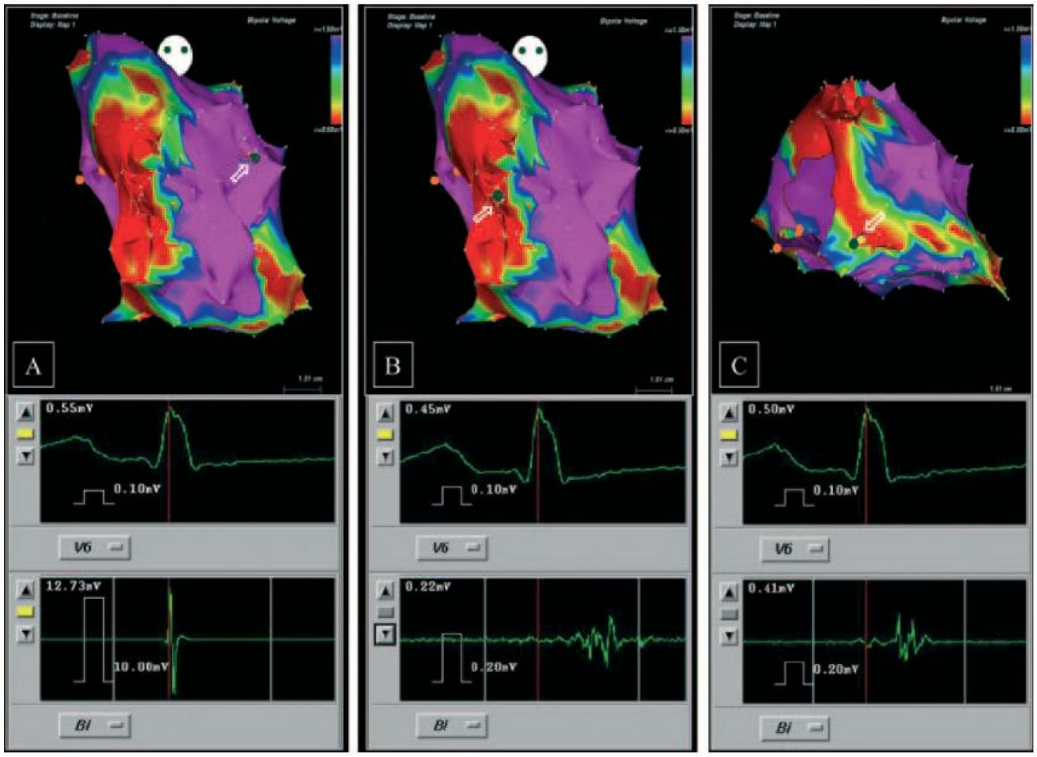


Figure 16 *Upper panels*: Three-dimensional electroanatomic voltage mapping of right ventricle in both anteroposterior (A and B) and bottom (C) views. *Bottom panels:* Electrograms recorded from areas with normal voltage (A), and from areas with low amplitude (B and C) in the same patient affected by arrhythmogenic right ventricular cardiomyopathy/dysplasia. Voltages are colour coded according to corresponding colour bars: purple represents signal amplitudes >1.5 mV (electroanatomic normal myocardium); red, <0.5 mV (electroanatomic scar tissue); and the range between purple and red, 0.5 to 1.5 mV (electroanatomic border zone). As indicated by the catheter tip (arrows), normal voltage electrogram sampled from the anterolateral region is sharp, biphasic deflection with large amplitude and short duration (bottom panel A). By comparison, low-voltage electrograms recorded from anterior and inferobasal regions are fragmented with prolonged duration and late activation (bottom panels B and C). From [84]: *Corrado D. et al.: Three-dimensional electroanatomic voltage mapping increases accuracy of diagnosing right ventricular cardiomyopathy/dysplasia. Circulation 2005; 11: 3042-3050.*

The low voltage area is more over investigated with high density mapping to obtain a greater accuracy.

Applications of 3-D electroanatomic voltage mapping

The 3-D electroanatomic voltage mapping has been introduced in the clinical practice nearly in the 1995. As previously explained, using different software it's possible to get maps of activation

and propagation, to study the origin and the characteristics of the arrhythmias, mesh maps to drive the ablation and voltage maps to identify the presence of the electrical signal in myocardium.

In the voltage mapping, the anatomical information are associated with the information about the amplitude of the electrograms recorded point by point with an electrode placed on the catheter tip. Thus we obtain a three-dimensional geometric reconstruction of the chamber of interest, with an overlapped colour-coded representation of voltage distribution (Fig. 17).

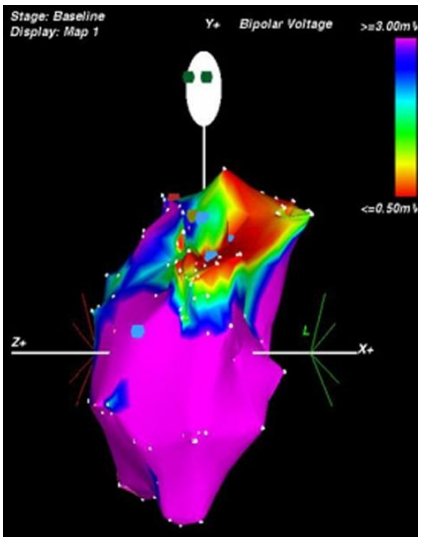


Figure 17 Electronatomic voltage mapping of right ventricle; it shows the presence of electroanatomic scar (in red colour), at outflow tract. From [110]: Folino A.F., Daliento L. "Arrhythmias after tetralogy of Fallot repair"-Indian Pacing Electrophysiol J 2005; 5(4): 312-324.

The electroanatomic scar area is defined as an area <1 cm^2 including at least 3 adjacent points with bipolar signal amplitude <0.5 mV and is depicted with red colour. Generally near to the electroanatomic scar, there isn't a normal tissue with normal voltage values, but rather a tissue with intermediary values (the so-called border zone).

Boulus et al. [83] has demonstrated that also in healthy subjects the colour distribution it is not homogeneous. In fact the septum presents the most elevated voltages, while the right ventricular outflow tract shows inferior voltages, and the right ventricle presents inferior voltages than the left ventricle. These differences are probably due to the greater thickness of the interventricular septum in comparison to the ventricular free walls and to the heterogeneous fatty distribution in the right ventricle.

The advantages of this technique is fully revealed in the context of the arrhythmogenic right ventricular cardiomyopathy showing the presence of electroanatomic scar, you mainly localized at the level of "triangle of the dysplasia" (inferior wall, apex and right ventricular outflow tract). The

finding of low voltage areas which correspond to the areas involved by the disease, is explained by the same nature of ARVC: the myocardium electrically active is replaced by electrically silent fibro-fatty tissue [83,84]. Thus the voltage mapping allows to carefully identify the presence, the location and the extent of this pathological substrate [83].

The diagnostic value of this technique for the arrhythmogenic right ventricular cardiomyopathy has been compared with the other instrumental investigations. It has been demonstrated that there is a correspondence between the electroanatomic scar and the akynetic and diskynetic regions by the bidimensional echocardiogram and the angiography [83,84], as well there is a relationship between the right ventricular free wall thinning, the aneurysms and the fatty infiltration shown by the cardiac magnetic resonance [83,85].

As previously mentioned, the early stages of ARVC, even presenting an increased risk of sudden death, show focal and mild structural abnormalities witch, often, are not detectable by the conventional investigations, as the echocardiography and angiography. It is clear instead, that, even if with a poorly clinical manifestation, the voltage mapping can show pathological abnormalities also in the earliest stages of the disease.

The cardiac MRI is very useful diagnostic investigation, but with undeniable limitations as the inter-observer variability and the difficulty, in some cases, to distinguish physiological findings of the fatty distribution from the true fatty infiltration [46,86].

However the endomyocardial biopsy represents the gold standard for the diagnosis. Nevertheless also this technique has some limitations: the arrhythmogenic right ventricular cardiomyopathy is, over all in the early stages, may present a focal distribution [54], and it rarely affects the interventricular septum; therefore the biopsy sampling, generally performed in limited area between the septum and the right ventricular anterior wall (to reduce the risk of perforation of the fragile thin free wall of this chamber [87]), can be negative.

In comparison to the biopsy, the electroanatomic voltage mapping is able to investigate a wider RV surface (the operator can decide the number of sampled points) and it is not limited by the focal distribution of the lesions in the early stages of the disease.

Corrado et al. [10] has found a significant correlation between the presence of the electroanatomic scar and the fibro-fatty replacement documented by the biopsy, concluding that an abnormal voltage map has a sensibility of 100% and specificity of 95% to identify the patients with positive endomyocardial biopsy.

For some aspects the three-dimensional electroanatomic mapping appears superior than the ventricular-coronary angiography. During the cardiac contraction the mobility of the right ventricle is not uniform, because the tricuspid area presents greater mobility in comparison to the anterior and

infundibular regions, which can alter the results of the ventricular-coronary angiography; this problem does not concern the three-dimensional electroanatomic mapping which evaluates the electric effects and not those mechanics secondary by the loss of the cardiomyocites [10].

Besides the endocardial mapping is very important to establish the differential diagnosis between the arrhythmogenic cardiomyopathy and its phenocopies (Fig. 18), i.e. pathologies with analogous clinical presentation and instrumental findings (ECG, echocardiography), as the sarcoidosis and the myocarditis. In fact the electroanatomic scars has been found in the arrhythmogenic cardiomyopathy, corresponding to areas of myocardial depletion and correlating with histopathological finding of myocardial atrophy and fibrofatty replacement at endomyocardial biopsy, but not in myocarditis, characterized by inflammatory pattern, with or without the necrosis of the cardiomyocites (according to the Dallas criteria).

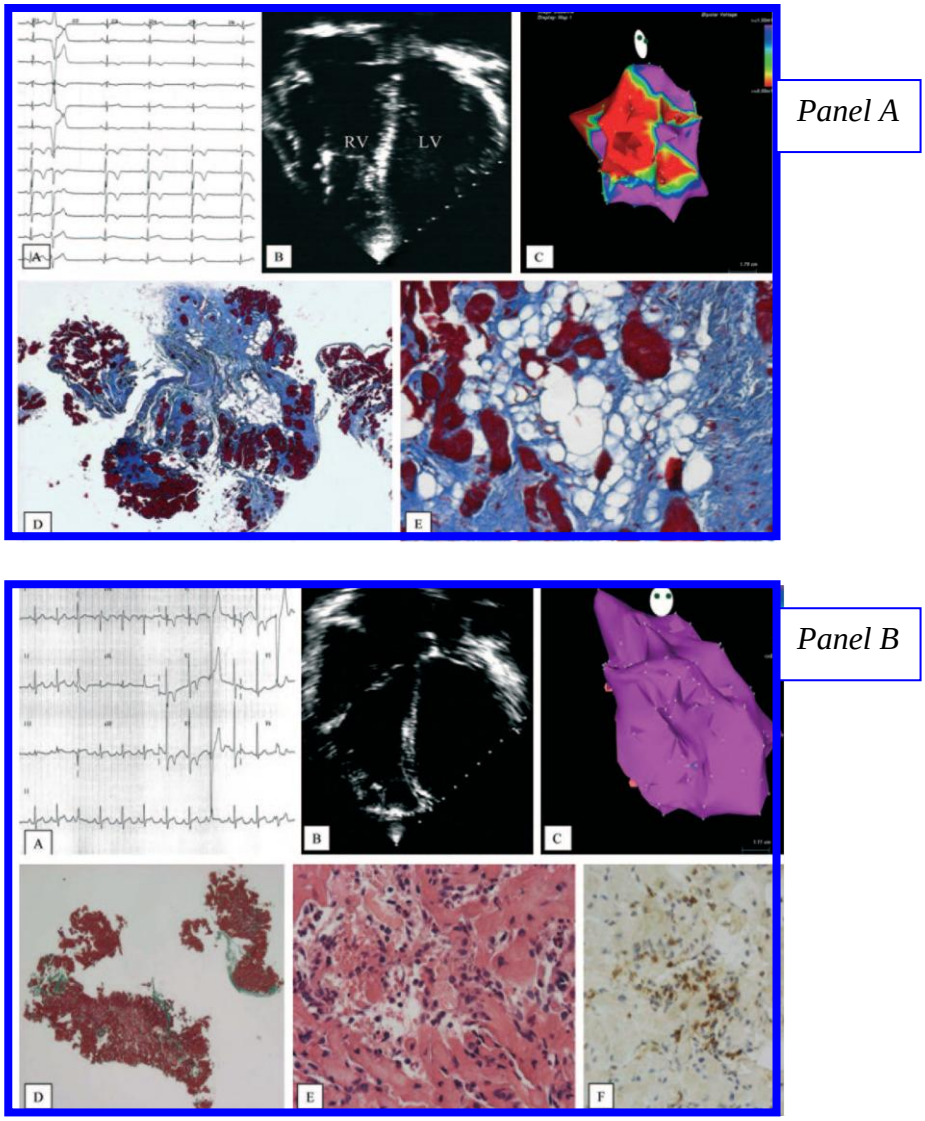


Figure 18 Comparison between the results of investigations, invasive and not invasive, in a patient with abnormal electroanatomic voltage map (*panel A*) and normal electroanatomic voltage map (*panel B*). Even if the clinical presentation (premature ventricular beats with QRS complex with LBBB morphology, A.) and echocardiographic findings (severe right ventricular dilatation, B) are quite identical, the electroanatomic voltage maps (C) differs between the two patients. In *panel A* the electroanatomic voltage map shows the presence of electroanatomic scar in anteroinfundibular, inferobasal and apical regions, which corresponds to areas of myocardial depletion and correlating with histopathological finding of myocardial atrophy and fibrofatty replacement at endomyocardial biopsy (D,E). In *panelB* instead to the electroanatomic voltage map (C) shows preserved bipolar voltages values areas and the endomyocardial biopsy (D,E,F) shows mild interstitial and enocardial fibrosis, the presence of inflammatory infiltrates and myocite necrosis, typical findings of myocarditis. From [84]: *Corrado D., Basso C. et al "Three-dimensional electroanatomic voltage mapping increases accuracy of diagnosing right ventricular cardiomyopathy/dysplasia". Circulation 2005; 11: 3042-3050.*

However, it is rightful to signal the study of Pieroni et al. [54] in which 30 with a noninvasive diagnosis of ARVC according to current criteria, underwent 3-dimensional EAM-guided EMB. Twenty-nine (97%) of 30 patients presented an abnormal voltage map. Histology and immunohistochemistry confirmed the diagnosis of ARVC in 15 patients, and showed active myocarditis according to Dallas criteria in the remaining 15 patients.

Thus it remains the question on the real ability of the electroanatomic mapping to distinguish between the inflammatory and degenerative patterns. Probably the conflicting results of this study are attributable to the fact that the inflammatory process, if still in action during the investigation, can determine some structural abnormalities interpreted by the endocardial voltage mapping as low amplitude areas.

However, the endocardial electroanatomic mapping has been demonstrated to have an important diagnostic role in the context of the ventricular arrhythmias. This technique, by using the activation and propagation maps, allows to individualize the origin of arrhythmia and, unlike the electrophysiological study, allows to identify accurately its anatomical substrate. In addition, when the electronatomic mapping is applied to ablation, it avoids the use of fluoroscopy to drive the catheter [88] because every mapped point is recorded and it's possible to conduct the catheter in the same ways.

Finally, the finding of electroanatomic scars allows a differential diagnosis between the two most important causes of ventricular tachycardia originating from the right ventricular outflow tract: the arrhythmogenic cardiomyopathy and the idiopathic tachycardia [10,89,90]. In the first case the endocardial mapping finds the presence of electroanatomic scars, while in the second one it does not because of the absence of any structural abnormality (Fig. 19). As previously explained, it's very important to make a distinction between these two pathologies, because, even if they can present the same clinical feature, they have extremely different prognosis: the idiopathic tachycardia has generally a favourable outcome [12], while the right ventricular arrhythmogenic cardiomyopathy/dysplasia implies a serious risk of sudden death.

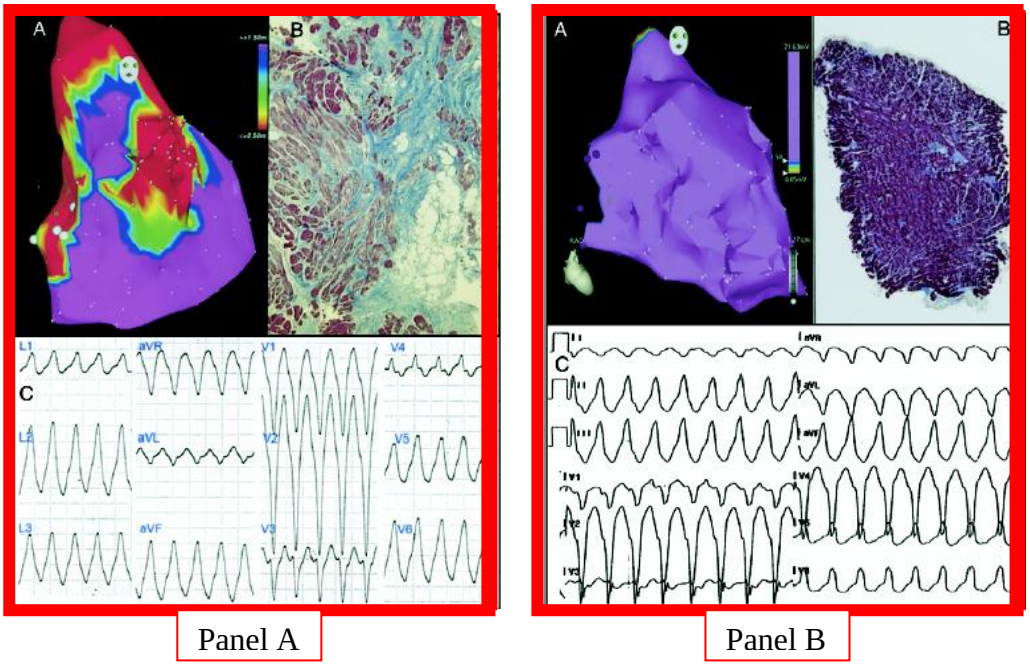


Figure 19 Comparison between the right ventricular electroanatomic bipolar voltage map in right anterior oblique view and endomyocardial biopsy of two patients presenting ventricular tachycardia with LBBB/inferior axis morphology (C). In *panel A* the electroanatomic voltage map (A) shows the presence of electroanatomic scar in the antero-infundibular region (**red** indicates < 0,5 mV):, which corresponds to fibrofatty replacement at endomyocardial biopsy (B). In *panel B* the voltage map (A) shows a homogeneous distribution of preserved bipolar voltage values (**purple** indicates > 1,5 mV): endomyocardial biopsy sample (B) shows normal myocardium. From [10]: *Corrado D., Basso C. et al. "Three-dimensional electroanatomical voltage mapping and histologic evaluation of myocardial substrate in right ventricular outflow tract tachycardia". J Am Coll Cardiol 2008; 51: 731-739.*

Nevertheless, endocardial electroanatomic mapping, even if presents clear advantages, shows also some limitations. This invasive technique implies all the risks of cardiac catheterization: femoral access complications (haematoma, thrombophlebitis, arteriovenous fistula), troubles of the rhythm (atrial/ventricular block, atrial fibrillation, malignant ventricular arrhythmias), transitory pericardial bleeding. Moreover, it must be considered the relevant price (approximately 2.500 euros/patient) and the time required to perform the investigation (more or less thirty minutes).

THIRD CHAPTER

Diagnostic value and prognostic implications of the three-dimensional electroanatomic mapping in patients with arrhythmias with right ventricular origin

OBJECTIVES

The electroanatomic voltage mapping with CARTO system allows to identify and characterize (presence, site and extent) the electroanatomic scar (EAS), that is a region of ventricular myocardium characterized by low electric voltage representing a possible substrate for life-threatening ventricular tachycardias.
The diagnostic role of this technique is largely approved:1) to identify the arrhythmic substrate, 2) during the ablation therapy of ventricular arrhythmias 3) for the differential diagnosis of arrhythmias originating from the right ventricle (idiopathic or associated with cardiomyopathies). It remains instead to establish the value of the technique for the risk stratification of arrhythmic sudden death.

The present study was designed to evaluate in a large number of patients with ventricular arrhythmias originating from right ventricular outflow, the:

- Prevalence of electroanatomic scar in patients with right ventricular arrhythmias.
- Relation between clinical data and presence/absence of the scar.
- Relation between the **presence** of electroanatomic scar, clinical data, ECG and hemodynamic parameters and the arrhythmic events during the follow-up.
- Predictive value of clinical, electrocardiographic, hemodynamic and electrophysiologic variables (including the electroanatomic scar) for arrhythmic events during follow-up.
- Relation between the **scar extent** and arrhythmic events during the follow-up.

METHODS

The study population consisted of 109 consecutive patients (73 males and 36 females) with a mean age of 36±14 years, with a left bundle branch block pattern ventricular arrhythmia, suggesting a RVOT origin.

The patients underwent detailed clinical evaluation with accurate personal history and non-invasive examinations such as electrocardiogram (ECG), 24 hours-Holter ECG, signal averaged ECG (SAECG) and bidimensional echocardiogram. Subsequently, patients underwent invasive studies like as ventricular-coronary angiography, endomyocardial biopsy, high density

electroanatomic voltage mapping with CARTO system and electrophysiological study with ventricular programmed stimulation.

In collecting patient history we payed particular attention to patient familiarity with best regard to juvenile sudden death (before 40 years old) or ARVC/D familiarity. During the first visit symptoms as palpitations and presence of syncope were harvested.

The 12-leads surface ECG and the Holter monitoring are been performed with the purpose to confirm and to characterize the arrhythmia.

The presence of late potential has been investigated with the SAECG using three different filters (20, 40 and 80 Hz) with a positive diagnosis with at least two of the following criteria:

- filtered QRS dispersion ≥114 msecs;
- prolongation > 38msec of late signals with amplitude ≤40 μVs (LAS 40);
- square root of the mean amplitude of the last 40 msecs of the QRS ≤20 μVs.

All patients have been investigated with bidimensional echocardiography to evaluate dimensions and global and segmental kinetics of both the ventricles (end diastolic volume corrected for the body surface and ejection fraction).

The left and right ventricular cineangiography and coronary angiography has been performed from the vein or from the femoral artery with the Seldinger technique. The ventricles have been examined by injection of contrast media and through fluoroscopic-ray imaging with anterior, left and right oblique projections.

The purpose of this exam was, as for echocardiography, to identify the presence of dilation, systolic dysfunction or regional anomalies of kinetic.

Endomyocardial biopsy (EMB) of the RV was obtained via the femoral vein with the use of the long sheath technique (disposable Cordis bioptome) in all patients. The samples were obtained at the junction between the ventricular septum and the anterior RV free wall. Three to 5 biopsy specimens were obtained from each patient, fixed in 10% phosphate-buffered formalin (pH 7.35), and then processed for histological examination. Seven-micrometer-thick paraffinembedded sections were serially cut and stained according to the hematoxylin-eosin and Heidenhain trichrome techniques. Histopathological diagnosis of ARVC/D was made on the basis of a significant amount of fibrofatty myocardial atrophy evaluated by histomorphometric analysis [91].

Electrophysiological study comprised programmed ventricular stimulation performed according to Wellens's protocol. All antiarrhythmic drugs were discontinued ≥5 half-lives (≥6 weeks for amiodarone) before the study. The stimulation protocol was performed with a minimum of 2 drive-cycle lengths and up to 3 ventricular extrastimuli while pacing from 2 right ventricular sites.

The stimulation protocol was repeated after intravenous isoprenaline infusion (with a dose of 2-6 μg/min) to evaluate why ventricular tachycardia was not inducible. Programmed ventricular stimulation was considered positive if a sustained ventricular tachyarrhythmia (such as mono- or poly-morphic ventricular tachycardia, ventricular flutter or ventricular fibrillation), ie, one that lasted ≥ 30 seconds or required termination because of hemodynamic compromise, was induced.

All patients underwent 3D electroanatomic voltage mapping technique by the CARTO system (Biosense-Webster) during sinus rhythm, as previously reported [92-100]. The magnetic mapping system includes a magnetic sensor in the catheter tip that can be localized in 3D space with the ultralow magnetic field generators placed under the fluoroscopic table. A 7F Navi-Star catheter, which consisted of 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 catheter. The catheter was placed at multiple sites on the endocardial surface to record bipolar electrograms from RV inflow, anterior free wall, apex, and outflow (with a mean of 197±23 sampled points). The bipolar signals were filtered at 10 to 400 Hz and were displayed at 100-mm/s speeds on the CARTO system. Bipolar electrograms were analyzed with regard to amplitude, duration, relation to the surface QRS, and presence of multiple components. The initial mapping points were sampled under fluoroscopic guidance to provide the outliers of the RV chamber geometry; thereafter, the mapping catheter was manipulated primarily by the CARTO system with fluoroscopy used only secondarily (mean, 9±1.2 minutes). A recording was accepted and integrated in the map when the variability in cycle length, local activation time stability, and maximum beat-to-beat difference of the location of the catheter were <2%, <3 ms, and <4 mm, respectively [96].

These parameters, combined with impedance measurements, were used to exclude signals with low amplitude due to poor endocardial catheter contact. In addition, adequate catheter contact was confirmed by concordant catheter tip motion with the cardiac silhouettes on fluoroscopy. The peak-to-peak signal amplitude of the bipolar electrogram was measured automatically. A 3D geometry of the RV chamber depicting the peak-to-peak amplitude of the bipolar electrograms recorded at each site was constructed in real time with the electrophysiological information colour coded and superimposed on the reconstruction.

Mapping points were acquired until a complete electroanatomic map of the RV had been generated. The voltage maps were edited, and intracavitary points, which were identified as sites located at abrupt indentations on the endocardial contour with associated sudden reduction in electrogram amplitudes compared with signals from surrounding sites, were eliminated. According to previous experiences on intraoperative [99] and catheter mapping [94,95,98-100]

"electroanatomic scar" area was defined as an area ≥1 cm^2 including at least 3 adjacent points with bipolar signal amplitude <0.5 mV. The colour display for depicting normal and abnormal voltage myocardium ranged from red, representing electroanatomic scar tissue (amplitude <0.5 mV), to purple, representing electroanatomic normal tissue (amplitude ≥1.5 mV). Intermediate colours represented the electroanatomic border zone (signal amplitudes between 0.5 and 1.5 mV). Regions showing low-amplitude electrograms were mapped with greater point density to delineate the extent and borders of electroanatomic scar areas.

The extent of EAS has been estimated by using an area calculation computer program. The all extent of EAS has been determined as the sum of RV low amplitude areas and expressed as percent RV area (Figure 20).

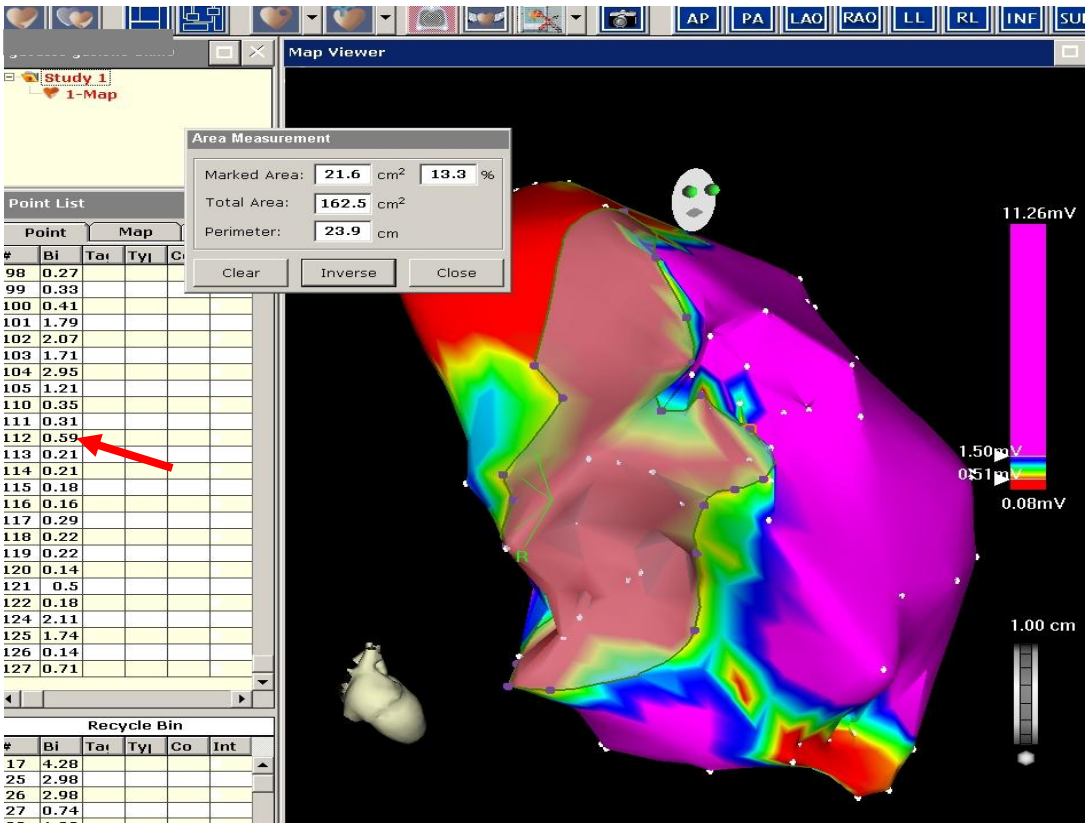


Figure 20: electroanatomic voltage map (right anterior oblique view of the right ventricle). The extent of electroanatomic scar (EAS) has been estimated by using an area calculation computer program. The all extent of EAS has been determined as the sum of RV low amplitude areas and expressed as percent RV area. The red arrow indicates two columns: the left one shows the progressive number of sampled points and the right one shows the corresponding bipolar voltage amplitude values.

According to current guidelines [101], ICD (implantable cardioverter defibrillator) was implanted in 19 patients for primary or secondary prevention of sudden death.

During a mean follow-up period of 49±13 months, patients were followed by periodical examinations, ECG and ICD interrogation. We collected malignant arrhythmic events such as sudden death, cardiac arrest due to ventricular fibrillation in , appropriate ICD intervention, and instable VT leading to syncope.

For Statistical Analysis, continuous variables are expressed as range and mean SD. Categorical differences between groups were evaluated by Fisher exact
text or χ^2 test. Differences between group means were compared by unpaired *t* test. All probability values reported are 2 sided, and a probability value <0.05 was considered statistically significant. SPSS software was used for statistical analysis.

RESULTS

The study population consisted 109 consecutive patients (73 men and 36 women) with a mean age of 36±14 years with a ventricular arrhythmia originating from right ventricle.

Clinical and instrumental findings

Clinical characteristics and instrumental findings are summarized in Tab.5.

Patients presented a mean age of 35,58 ± 14,13 years and were primarily males (67% of the sampled population). Twenty-six (24%) patients had a family history of sudden death and/or of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D). Sixty-eight (62%) patients were symptomatic for palpitations and 22 (20%) for syncope. Clinical arrhythmias were frequent and/or ripetitive premature ventricular beats (defined as ≥ 5 premature ventricular in 1 minute at standard ECG or as ≥ 10-30 ventricular beats in 1 hour under continuous recording) in 24 (22%), non sustained VT (NSVT) (defined as > 6 consecutive ventricular beats, which length was inferior than 30 seconds) in 64 (59%) and sustained ventricular tachycardia (SVT) (with a duration more than 30 seconds) in 21 (19%) patients. SAECG was positive for the presence of late potentials in 39 (36%) patients.

Right ventricular ejection fraction (RVEF) observed at echocardiography, was 53±8,42 while RV end diastolic volume was 78±25,78 ml/m^2 . In left ventricle ejection fraction and end diastolic volume were respectively 58,09±7,64% and 65,07±15,10 ml/m^2. Electrophysiologic study was performed in 69 (63%) patients and it was positive in 31/69 (45%). In 63 patients, who were been submitted to endomyocardial biopsy, histological analysis of EMB samples demonstrated a significant myocardial atrophy and fibrofatty replacement confirming the diagnosis of ARVC/D in 23. Of the remaining 40 patients, 9 were normal, 13 had EMB histopathological changes that were consistent with the diagnosis of inflammatory cardiomyopathy, 6 with primitive dilated cardiomyopathy and 4 with endocardiofybrosis (Table 8)

Electroanatomic scar: correlation between clinical variables and instrumental findings

Electroanatomic scars were found in 54 patients (49%) and affected a mean of 20.4±13% (range 2.6% to 49.8%) of the RV free wall.

Relation between electroanatomic scars and clinical variables is summarized in Table 5.

No significant correlation was found between the scar presence and the patients' age and sex: the mean age was 37,88 years in patients with EAS and 33,33 years in patients without scar; among patients with electroanatomic scar, males were 72% (39/54 patients) while, among patients without EAS, were 62% (34/55 patients).

We found a significant correlation between the presence of electroanatomic scar and positive family history (P=0.001): 21 (39%) patients with electroanatomic scar reported family history for sudden death or ARVC/D in respect to the five patients without EAS (9%). This data was confirmed considering separately sudden death (15 patients with EAS versus 5 without EAS; P=0,023) and positive history for ARVC/D (10 patients with EAS versus 2 patients without EAS; P=0,030), as showed in Table 6.

Symptoms referred by patients didn't significantly differ among the two groups (with or without electroanatomic scar): palpitations were perceived by 70% of patients with electroanatomic scar and by 55% of patients without; syncope was happened in 28% of patients with EAS while in 13% in patients without EAS.

SAECG, performed in 36% of study population, showed a significant correlation with the presence of electroanatomic scar (P=0,001): late potentials were present in 28 (52%) patients with scar and in 11 (20%) without scar.

At echocardiography, mild right ventricular involvement was diagnosed and it was significantly inferior in patients with electroanatomic scar (50,44%±8,87% in patients with EAS

versus 55,54%±7,19% in patients without EAS; P=0,0013, while end diastolic volume of right ventricle was significantly greater in patients with EAS than in patients without (respectively 85,98 ml/m^2 ± 30,27 ml/m^2 versus a 65,18 ml/m^2 ± 14,37 ml/m^2; P=0,001). For left ventricle, only ejection fraction differed between two groups resulting inferior in patients with EAS (56,41%±9,45%) in respect of patients without scar (59,74%±4,86%) (P=0,024).

Electrophysiological study was performed in 69 (63%). Seventeen patients with electroanatomic scar (52 %) were inducible, while 14 (39%) patients without electroanatomic scar had a positive programmed ventricular stimulation. No correlation was found in this case.

EMB was performed in 63 patients (58%). Histological analysis of EMB samples demonstrated a statistical correlation (P<0,001) between the presence of electroanatomic scar and ARVC/D feature: 22 (58%) of patients with EAS were affected by ARVC/D, while only one (4%) of patients without EAS had this finding. It hasn't been found a significant correlation between the presence of electroanatomic scar and the histopathological findings (Table 8).

Follow-up

Patients were followed during a mean follow-up period of 49±13 months to evaluate the appearance of arrhythmic events.

During the observation period 25 of 109 patients (23%) experienced malignant arrhythmic events such as:

- sudden death in 2 patients (8%),
- cardiac arrest due to ventricular fibrillation in 4 patients (16%),
- appropriate ICD interventions in 7 patients (28%)
- instable ventricular tachycardia leading to syncope in 12 (48%).

Bottom, it is showed the Kaplan Mayer curve of the arrhythmic events during follow-up between patients with electroanatomic scar and patients without (Fig. 21)

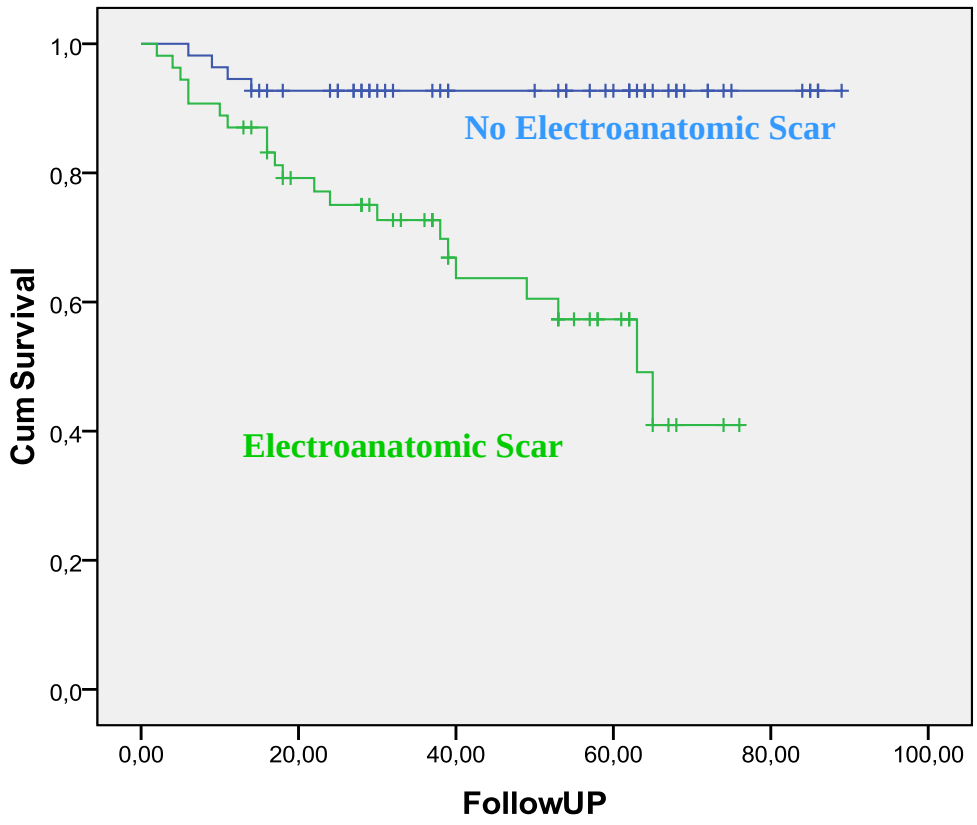


Fig. 21 Kaplan Mayer curve of the arrhythmic events during follow-up between the two comparing groups (patients affected by electroanatomic scar and patients without electroanatomic scar)

Of different clinical variables, electrocardiographic, hemodynamic and electrophysiological (including electroanatomic scar) predictive value was analyzed to evaluate arrhythmic events in the follow-up (Table 9).

At univariate analysis, electroanatomic scar ($p<0.001$) and unexplained syncope ($p<0.001$) were significantly associated with the arrhythmic events, in particular 60% of patients reported a syncope event versus 8% of patients without ($P<0,001$).

In regard to the relation between electroanatomic scar and arrhythmic events the presence of EAS was well documented in 84% of patients with arrhythmic events and in 39% patients without.

A sub-analysis for different arrhythmic events demonstrated a statistically significant relation between electroanatomic scar and appropriate ICD interventions ($P=0,018$) and between electroanatomic scar and ventricular tachycardia leading syncope ($P=0,024$) (Table 7 e Fig.s 22 e 23).

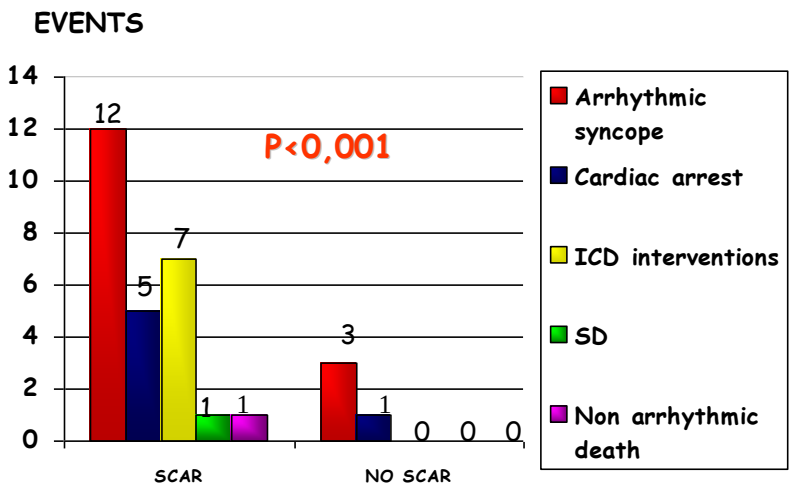


Figure 22 Arrhythmic event distribution during follow-up between two comparing groups. ICD, implantable cardioverter defibrillator; SD, sudden death.

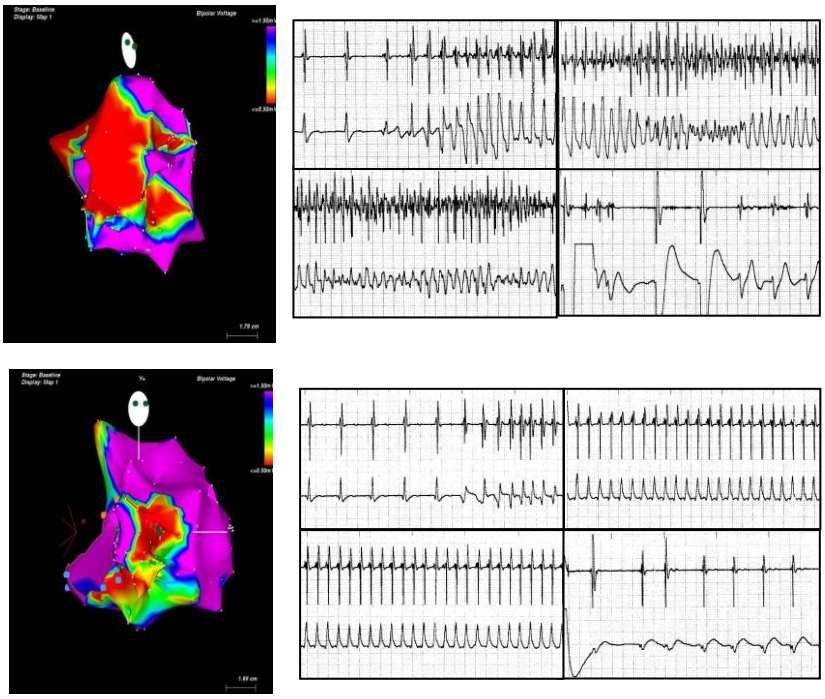


Figure 23 Appropriate ICD interventions in 2 patients with electroanatomic scar. *Upper panel:* at electroanatomic voltage map the left anterior oblique projection clearly shows electroanatomic scar involving about 50% of right ventricular free wall. ICD (on the right) has recognized a ventricular fibrillation episode and, with shock therapy, was able to interrupt it. *Bottom panel:* an episode of ventricular flutter interrupted by shock therapy (on the right) in a patient with a 30% EAS area at electroanatomic voltage mapping (on the left). ICD, implantable cardioverter defibrillator

It was not been found any predictive value between arrhythmic events during follow-up and other variables (i.e. age, sex, family history for juvenile sudden death or for arrhythmogenic right ventricular cardiomyopathy, palpitations, kind of arrhythmias, late potentials, echocardiographic parameters and electrophysiological study) (Table 9). Therefore no correlation was found between the right ventricular regions affected by EAS and malignant arrhythmic outcome (Table 10).

At multivariate analysis, after adjustment for age, family history, VT, and RV dilatation/dysfunction, unexplained syncope (OR=15.9, 95%CI=4.1-61.8; p<0.001) and RV electroanatomic scars (OR=9.28, 95% CI=2.0-42.7; P=0.004) remained independent predictors of malignant arrhythmic outcome (Table 11).

Relation between electroanatomic scar extent and arrhythmic events

We observed a significant correlation between the presence of electroanatomic scar extent and the appearance of arrhythmic events during follow-up (P<0,001): among patients with an abnormal right ventricular electroanatomic voltage mapping (RV EVM), those who experienced arrhythmic events during follow-up had a significantly greater percentage of electroanatomic scar (27.4±10.5%) while patients without arrhythmic events had RV EVM of 16±12.3%, with P<0.001 (Table 12 and Fig. 24). Bottom, it is showed the Kaplan Mayer curve of the arrhythmic events during follow-up between the two comparing groups (Fig 25).

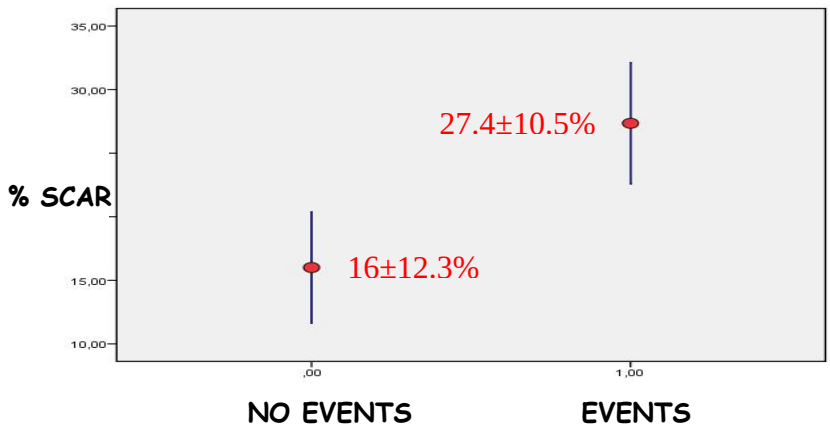


Figure 24 Electroanatomic scar extent expressed as percent area of right ventricular free wall between two comparing groups. Data are evaluated as mean ± standard deviation.

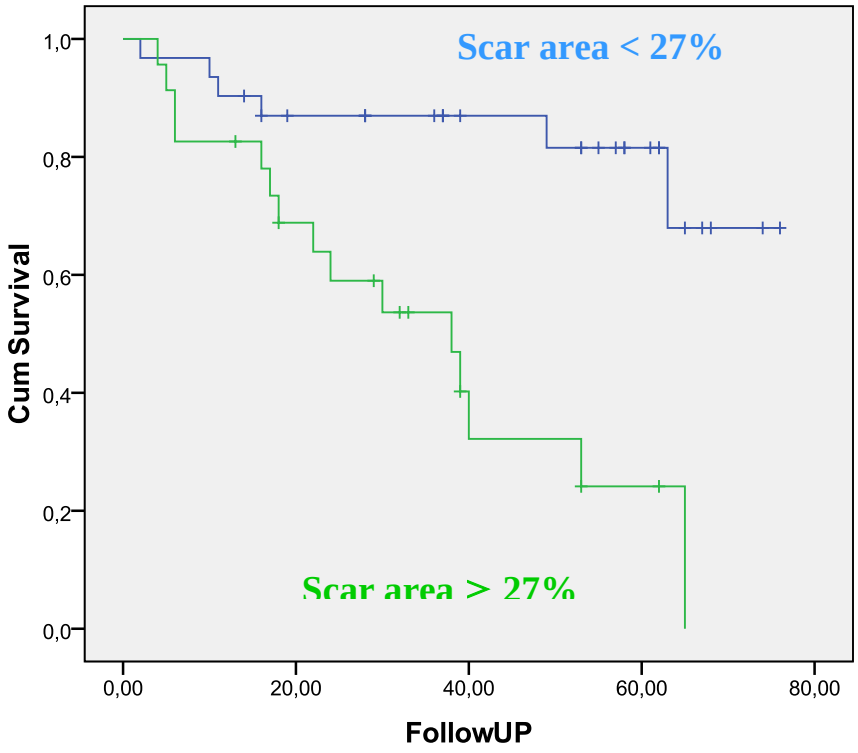


Fig. 25 Kaplan Mayer curve of the arrhythmic events during follow-up between the two comparing groups

DISCUSSION

Endocardial voltage mapping (EVM) by CARTO system offers the potential to accurately identify the presence, location and extent of right ventricular (RV) low-voltage regions (i.e. electroanatomic scars) which may represent the substrate of life-threatening right ventricular tachyarrhythmias. The diagnostic role of 3D electroanatomic voltage mapping (EVM) has been already demonstrated for RV abnormalities [80-84,88,89]. It has been demonstrated, also, its critical role for the differential diagnosis of ventricular tachyarrhythmias originating from right ventricle [10,84,89] such as idiopathic tachycardia and ventricular arrhythmias leading to cardiomyopathies. Particularly, the technique reliably identifies and characterizes low-voltage regions which in patients with ARVC/D correspond to areas of myocardial depletion and correlate with the histopathological finding of myocardial atrophy and fibrofatty replacement at endomyocardial biopsy (EMB).

Whether electroanatomic voltage mapping may help in the risk stratification [110] of patients with RV arrhythmias remains to be elucidated. This study was designed to prospectively evaluate the prognostic value of RV electroanatomic scar in a cohort of patients presenting clinically with arrhythmias of RV origin. The major study results are that electroanatomic scars are found in approximately half of patients with significant arrhythmias of right ventricular origin; there is a significant correlation between the electroanatomic scars and positive family history, late potentials and RV dilatation/dysfunction; there is a significant correlation between electroanatomic scar extent and incidence of arrhythmic events during follow-up; therefore, electroanatomic scar, unlike RV dilatation/dysfunction, is an independent predictor of malignant arrhythmic outcome.

Prevalence of RV scar

In the study population the prevalence of electroanatomic scar was 49%.

The high prevalence of the electroanatomic scar in patient presenting arrhythmias with right ventricular origin is partly justified by the selection of the patients. In other words there is a bias of selection that involves an elevated pre-test probability to find the electroanatomic scar while in the most greater part of the cases the right ventricular arrhythmias are idiopathic tachycardia without association with a structural abnormalities of the myocardium.

Correlation between clinical data and the presence/absence of the electroanatomic scar

There was a significant correlation between the presence of electroanatomic scar and positive family history for sudden death and ARVC/D both together (P=0.001) also when were calculated separately (respectively P=0,023 and P=0,030).

Arrhythmogenic right ventricular cardiomyopathy and idiopathic tachycardia are the most common responsible of arrhythmias originating from right ventricular outflow; idiopathic RV tachycardia is a non-familial and benign condition that occurs in young individuals without structural heart disease while ARVC/D is a structural and eredo-familial disease.

Then, the association between the presence of electroanatomic scar and the positive family history may exclude idiopathic ventricular tachycardia as responsible of ventricular arrhythmias in the study population. An other result of this study confirms the same concept: there was a significant correlation between the histological finding of ARVC/D and the presence of electroanatomic scar.

Our data are in agreement with previous scientific literature data, in fact, Corrado et al. that reported a sensitivity of 100% and specificity of 95% of electroanatomic mapping to identify fibro-fatty replacement (confirmed by endomyocardial biopsy) [10].

We observed a significant correlation (P=0,001) between electroanatomic scar and late potentials at Signal-Averaged-ECG. The presence of late potentials reflects the conduction dispersion of electric signal due to cardiomyocytes localized in connectival tissue. The occurrence of late potentials confirms the structural damage that may represent an arrhythmogenic substrate and might be considered an ECG analogue of electroanatomic scar.

Finally, there was a significant correlation between electroanatomic scar and right ventricular dysfunction (P=0,0013) and dilation (P<0,001) and between EAS and left ventricular dysfunction (P=0,024). These data support the concept that greater the RV hemodynamic impairment higher the probability of electroanatomic lesions.

Prognostic value of RV scar

The present study is the first one evaluating the prognostic value of RV electroanatomic scar.

The presence of electroanatomic scar significantly correlated with arrhythmic events appearance during follow-up (P<0,001): 84% of patients who experienced malignant arrhythmic events, presented electroanatomic scar.

Therefore, there was a significant correlation (P<0,001) between electroanatomic scar extent and malignant arrhythmic events during follow-up. These results demonstrate that EAS can be considered as an arrhythmogenic substrate and show its positive predictive value for arrhythmic events.

At multivariate analysis, corrected for age, family history, ventricular tachycardia and right ventricular dilatation/dysfunction, RV electroanatomic scars remained a strong and independent predictor of malignant arrhythmic outcome (P=0,004).

Prognostic value of RV scar extent

There is a significant correlation between the presence of electroanatomic scar extent and the appearance of malignant arrhythmic events during follow-up (P<0,001). The cut-off of electroanatomic scar extent corresponds to near 27±10% of the free right ventricular wall. EASs with extent higher than this value present a worse prognosis.

Limitations of the procedure

This technique employs an invasive procedure and so it includes some adverse events, i.e. haematoma, artery-venous fistulas and pericardial effusion or tamponade. Any way, in our study, we don't observe adverse events. The method is not available in all EP-labs (electrophysiological laboratories), but only in those of third level and it can be applied as last investigation and only on selected patient. Besides the voltage mapping, virtually valid for all the cardiac chambers, is applied in a greater percentage of cases only to the right ventricle. Even if in our work we have studied only the right ventricle (since we have studied the arrhythmias from the right ventricle) it would be interesting to evaluate also the left ventricle (especially in right ventricular arrhythmogenic

cardiomyopathy with biventricular involvement or in the rare cases of arrhythmogenic cardiomyopathy with exclusively left ventricular involvement). The evaluation of the left ventricle would ask the puncture of the femoral artery with a greater risk of adverse events, a longer haemostasis (24 hours instead that few hours as in the case of the puncture of the femoral vein) and a higher risk of adverse events on the aortic valve (for the rigidity of the catheter positioned by retrograde aortic way) and greater time of fluoroscopy.

For this reason it is very higher the interest for not the invasive techniques as the MRI even if, as already mentioned, this technique still shows some limitations for the study of the right ventricle as the inter-observer variability and the difficulty, in some cases, to distinguish physiological findings of the fatty distribution from the true fatty infiltration [46,86].

CONCLUSIONS

The present study confirms the diagnostic role of endocavitary electroanatomic voltage mapping to identify the anatomical substrate of right ventricular tachyarrhythmias.

In addition, we demonstrated the prognostic value of this technique, allowing a best stratification of arrhythmic risk among patients presenting right ventricular arrhythmias.

So, the presence of electroanatomic scars, particularly if extended, allows a best identification of the candidates of prophylactic ICD implantation among the wide population with arrhythmias originating from right ventricle.

Table 5 Correlation between electroanatomic scar and clinical variables and instrumental findings. Data are expressed as absolute numbers and percent of study population. Continuous variables are evaluated as mean ± standard deviation.

	All patients (n=109)	**Patient WITH SCAR (n=54)**	**Patient WITHOUT SCAR (n=55)**	**P**
Age	35,58 ± 14,13	37,88	33,33	0,0917
Sex	73 (67%)	39 (72%)	34 (62%)	0,342
Family history	26 (24%)	21 (39%)	5 (9%)	**0,001**
Palpitations	68 (62%)	38 (70%)	30 (55%)	0,132
Syncope	22 (20%)	15 (28%)	7 (13%)	**0,086**
PVB	24 (22%)	12 (22%)	12 (22%)	0,981
SVT	21 (19%)	14 (26%)	7 (13%)	0,22
NSVT	64 (59%)	31 (57%)	33 (60%)	0,44
SAECG	39 (36%)	28 (52%)	11 (20%)	**0,001**
Inducibility at EPS	31/69 (45%)	17/33 (52%)	14/36 (39%)	0,41
RV-EF (%)	52,85 ± 8,46	50,44±8,87	55,54±7,19	**0,0013**
RV-EDV (ml/m^2)	75,39 ± 25,78	85,98±30,27	65,18±14,37	**<0,001**
LV-EF (%)	58,09 ± 7,64	56,41±9,45	59,74±4,86	**0,024**
LV-EDV(ml/m^2)	65,07 ± 15,10	66,25±14,30	63,90±15,90	0,418

PVB: premature ventricular beats; SVT: sustained ventricular tachycardia; NSVT: non sustained ventricular tachycardia; SAECG: signal averaged ECG; EF: ejection fraction; EDV: end diastolic volume; RV: right ventricle; LV: left ventricle, EPS: electrophysiological study.

Table 6 Correlation between electroanatomic scar and family history. Data are expressed as absolute numbers (with or without scar) in three different groups.

	Patient WITH SCAR (n=54)	**Patient WITHOUT SCAR (n=55)**	**P**
Patients with family history for sudden death (n=20)	15	5	0,023
Patients with family history for ARVC/D (n=12)	10	2	0,030
Patients with family history for sudden death + ARVC/D (n=26)	21	5	**0,001**

ARVC/D: arrhythmogenic right ventricular cardiomyopathy/dysplasia

Table 7 Correlation between electroanatomic scar and malignant arrhythmic outcome.

Arrhythmic event	**All population (n=109)**	**Patients WITH scar (n=54)**	**Patients WITHOUT scar (n=55)**	**P**
Arrhythmic syncope	15	12	3	**0,024**
Cardiac arrest	6	5	1	0,19
ICD interventions	7	7	0	**0,018**
Sudden death	1	1	0	0,99
Non arrhythmic death	1	1	0	0,99
All events	30	26	4	**0,000**
All events (without syncope)	15	14	1	**0,001**

ICD: implantable cardioverter defibrillator

Table 8 Correlation between electroanatomic scar and histopathological findings of endomyocardial biopsy (EMB) samples. Data are expressed as absolute numbers and percent of study population in six different groups.

Histological findings	**Patients performed to EMB, WITH SCAR (n=38)**	**Patients performed to EMB, WITHOUT SCAR (n=25)**	**P**
ARVC/D	22 (58%)	1 (4%)	**<0,001**
Suspect of ARVC/D and/or myocarditis	5 (13%)	5 (20%)	0,708
Primitive dilated cardiomyopathy	2 (5%)	4 (16%)	0,204
Inflammatory cardiomyopathy	6 (16%)	7 (28%)	0,393
Endocardiofybrosis	1(3%)	1(4%)	1,00
Negative	2 (5%)	7(28%)	**0,023**

ARVC/D: arrhythmogenic right ventricular cardiomyopathy/dysplasia

Table 9 Correlation between arrhythmic events appearance during follow-up and clinical variables and instrumental findings. Data are expressed as absolute number and percent of study population. Continuous variables are evaluated as mean ± standard deviation.

	All patients (n=109)	**Patients WITH EVENTS (n=25)**	**Patients WITHOUT EVENTS (n=84)**	**P**
Age	36±14,13	34,64±14,3	35,87±14,5	0,7
Sex	73 (67%)	19 (76%)	54 (64%)	0,39
Family history	26 (24%)	7 (28%)	19 (23%)	0,77
Palpitations	68 (62%)	14 (56%)	54 (64%)	0,61
Syncope	22 (20%)	15 (60%)	7 (8%)	**<0,001**
PVB	24 (22%)	3 (12%)	21 (25%)	0,271
SVT	21 (19%)	5 (20%)	16 (19%)	0,85
NSVT	64 (59%)	17 (68%)	47 (43%)	0,39
Prev. VT morph:				
LBBB/Inf. axis	60	13	47	0,9
LBBB/Sup. axis	37	10	27	0,6
SAECG	39 (36%)	10 (40%)	29 (35%)	0,79
RV-EF (%)	53 ± 8,42	51,68± 8,34	53,17 ± 8,41	0,43
RV-EDV (ml/m^2)	78±25,78	80,40±32,68	73,20±24,51	0,31
LV-EF (%)	58 ±7,64	57,04 ± 8,76	58,28 ± 7,34	0,51
LV-EDV (ml/m^2)	65 ±15,10	62,08±11,53	65,96±15,96	0,18
Inducibility at EPS	31/69 (45%)	11/17 (65%)	20/52 (38%)	0,11
Electroanatomic scar	54 (49%)	21 (84%)	33 (39%)	**<0,001**

PVB: premature ventricular beats; SVT: sustained ventricular tachycardia; NSVT: non sustained ventricular tachycardia; Prev.VT morph: prevalent ventricular tachycardia morphology; LBBB: left bundle branch block; Inf.axis: inferior axis; Sup.axis: superior axis; SAECG: signal averaged ECG; EF: ejection fraction; EDV: end diastolic volume; RV: right ventricle; LV: left ventricle, EPS: electrophysiological study.

Table 10 Correlation between electroanatomic right ventricular regions affected by electroanatomic scar regions and events appearance during follow-up. Data are expressed as absolute numbers and percent of study population.

EAS regions:	All patients (n=109)	Patients WITH EVENTS (n=25)	Patients WITHOUT EVENTS (n=84)	P
Basal-Posterior	28/54 (51%)	10/21 (47%)	18/33 (54%)	0,82
Inferior	23/54 (42%)	11/21 (52%)	12/33 (36%)	0,38
Anterolateral	29/54 (53%)	13/21 (61%)	16/33 (48%)	0,49
RVOT	26/54 (48%)	12/21 (57%)	14/33 (42%)	0,43
Apex	16/54 (29%)	7/21 (33%)	9/33 (27%)	0,86

EAS: electroanatomic scar; RVOT: right ventricular outflow.

Table 11 Multivariate analysis. OR, odds ratio; CI 95%, confidence interval at 95%.

Variable	OR	CI 95%	P
Unexplained syncope	15,9	4,1-61,8	**<0,001**
Electroanatomic scar	9,28	2,0-42,7	**0,004**

Table 12 Electroanatomic scar extent, expressed as percent area of right ventricular free wall in two comparing groups. Data are expressed as mean ± standard deviation.

	Population with scar (n=54)	Patients WITH EVENTS (n=25)	Patients WITHOUT EVENTS (n=84)	P
% Electroanatomic scar	20,41±12,83	27,35±10,47	16,00±12,34	**<0,001**

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LEGEND

AAD: antiarrhythmic drugs

AD: autosomal dominant

ALVC: arrhythmogenic left ventricular cardiomyopathy

AR: autosomal recessive

AV: atrio-ventricular

cAMP: cyclic adenosine monophosfate

DADs: delayed afterdepolarizations

DCM: dilated cardiomyopathy

EAM: electroanatomic mapping

EADs: early afterdepolarizations

EAS: electroanatomic scar

EDV: end diastolic volume

EF: ejection fraction

EPS: electrophysiological study

EVM: Endocardial voltage mapping

ICD: implantable cardioverter-defibrillator

Inf.axis: inferior axis

LBBB: left bundle branch block

LV: left ventricle, left ventricular

MRI: magnetic resonance imaging

NSVT: non sustained ventricular tachycardia

PKA: phosphokynase A

Prev.VT morph: prevalent ventricular tachycardia morphology

PVB: premature ventricular beats

PVS: programmed ventricular stimulation

RBBB: right bundle branch block

RMVT: repetitive monomorphic ventricular tachycardia

RV: right ventricle, right ventricular

RVOT: right ventricular outflow

SAECG: signal averaged ECG

SD: sudden death

SPVT: sustained paroxysmal ventricular tachycardia

Sup.axis: superior axis

SVT: sustained ventricular tachycardia

VF: ventricular fibrillation

VFl: ventricular flutter

VT: ventricular tachycardia

3-D: tree dimensional