

# Diagnostic Value of Cardiac Magnetic Resonance in Patients with Frequent Ventricular Arrhythmia and Normal Doppler Echocardiography.

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## ABSTRACT

### Introduction

Frequent ventricular arrhythmia can be a primary electrical disturbance or may be associated to cardiomyopathy. The prognostic and therapeutic impact depends on the presence of structural heart disease. Transthoracic Doppler echocardiography has been the most important complementary study to evaluate the presence of cardiac structural abnormalities.

### Objectives

The aims of this study were to determine the ability of cardiac magnetic resonance imaging to detect structural heart disease in patients with normal Doppler echocardiogram and to assess the incidence of adverse cardiovascular events during follow-up.

### Methods

The study included 66 consecutive patients with frequent ventricular arrhythmia defined as > 5000 ventricular extrasystoles in 24-hour Holter monitoring, ventricular tachycardia or resuscitated cardiac respiratory arrest with normal Doppler echocardiogram. All patients underwent cardiac magnetic resonance imaging to assess cardiomyopathies.

### Results

Fifty-seven percent of patients had structural heart disease. The most prevalent diagnosed pathologies were myocarditis sequelae, non-compacted myocardium and subendocardial infarction scar. At mean follow-up of  $24 \pm 22$  months, the incidence of adverse cardiovascular events was 6.06 %. The number of ventricular extrasystoles was higher in patients with abnormal cardiac magnetic resonance.

### Discussion

This work demonstrates that in patients with frequent ventricular arrhythmia and normal Doppler echocardiogram, gadolinium cardiac magnetic resonance imaging can detect structural heart disease in more than half of the cases. Patients with frequent ventricular arrhythmia during Holter monitoring, normal Doppler echocardiogram and mild alterations in the magnetic resonance present low risk of cardiovascular events.

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## Key words >

Magnetic Resonance Imaging - Arrhythmias, Cardiac - Cardiomyopathies

## Abbreviations >

<b>CMR</b>	Cardiac magnetic resonance	<b>NSVT</b>	Non-sustained ventricular tachycardia
<b>DGE</b>	Delayed gadolinium enhancement	<b>RV</b>	Right ventricular
<b>ECG</b>	Electrocardiogram	<b>SVT</b>	Sustained ventricular tachycardia
<b>FVA</b>	Frequent ventricular arrhythmia	<b>VE</b>	Ventricular extrasystoles
<b>ICD</b>	Implantable cardioverter defibrillator	<b>VT</b>	Ventricular tachycardia
<b>LV</b>	Left ventricular		

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## INTRODUCTION

Patients with frequent ventricular arrhythmia (FVA) must be evaluated to determine the presence or absence of structural heart disease, since the prognosis and therapeutic approach may vary accordingly. (1) Frequent ventricular arrhythmia can progress to dilated cardiomyopathy or be a prognostic marker in patients with underlying structural heart disease. The initial evaluation of these patients involves a full questionnaire, thorough physical examination, electrocardiogram, 24-hour Holter monitoring, exercise stress testing, and Doppler echocardiography. Until some years ago, the latter was the most important method to determine the presence of structural heart disease. (2) In selected patients, invasive methods such as electroanatomic mapping or endomyocardial biopsy, may be used. (3) Cardiac magnetic resonance imaging (CMR) is an established technique to evaluate changes in cardiac structure, assessing ventricular volumes, regional wall motion, global systolic function and tissue composition, differentiating fat, edema, necrosis and/or myocardial fibrosis. This study postulates that in patients with FVA and normal echocardiogram, CMR may detect previously unidentified significant structural heart disease.

## METHODS

### Population

A contrast CMR protocol was performed in 66 patients with FVA and normal Doppler echocardiogram to detect structural heart disease. Consecutive patients with any of the following ventricular arrhythmias were included: a) frequent ventricular extrasystoles (VE) defined as > 5000 VE in 24-hour Holter monitoring (n = 55), b) non-sustained ventricular tachycardia (NSVT), defined as ventricular rhythm of 3 or more ventricular beats lasting < 30 s and heart rate > 120 bpm without hemodynamic decompensation (n = 22), c) sustained ventricular tachycardia (SVT), defined as ventricular rhythm with heart rate > 120 bpm (n = 4) and lasting > or < 30 s with hemodynamic decompensation or d) resuscitated cardiac arrest (n = 1). Doppler echocardiography was considered normal in the presence of preserved transthoracic left ventricular (LV) systolic function and absence of significant valvular heart disease or LV hypertrophy (wall thickness > 1.3 cm). We excluded patients with FVA within 30 days of an acute coronary syndrome or FVA secondary to electrolyte imbalance.

### Study design

A contrast CMR was prospectively requested to rule out structural heart disease in all patients with FVA that met the selection criteria. Baseline characteristics and the incidence of clinical events in the study population were retrospectively recorded. Since the analysis corresponded to retrospective studies routinely performed in the medical practice of our hospital, informed consent was not requested for the study.

### Cardiac magnetic resonance protocol

Patients were examined in supine position on a 1.5 Tesla scanner after ensuring they had no endangering ferromagnetic material. A phased-array radiofrequency receiver coil was placed on the patient's chest. Cine-magnetic resonance

images were obtained in the long axes (4 chambers, 2 chambers and LV outflow tract) and short axes covering both ventricles from base to apex. All images were obtained with repeated breath-hold and ECG gating. Epicardial and endocardial borders were marked to obtain volume and mass of the heart chambers and calculations were performed using the Argus software (Siemens Inc.). In patients with suspected myocarditis, T2-weighted sequence images with triple reverse pulse were obtained to assess myocardial edema. Approximately 10 minutes after administration of 0.2 mmol/kg gadolinium (Magnevist®), delayed enhancement images were acquired in slices oriented to match the cine images using a standard, phase sensitive multisegment inversion pulse sequence. Manual adjustment of time inversion was performed to optimize image contrast. In those patients in whom the presence of frequent ventricular arrhythmia did not allow good quality images, volume and ejection fraction measurements were performed in real time cine-magnetic resonance sequences and single-shot delayed enhancement sequences.

### Cardiac magnetic resonance diagnosis and clinical events

Myocardial infarction was detected as presence of delayed gadolinium enhancement (DGE) with pattern and associated regional systolic dysfunction. Subepicardial or intramyocardial DGE focal patterns with signs of edema in T2-weighted images were interpreted as acute myocarditis and in the absence of signs of edema as a consequence of myocarditis. Non-compacted myocardium was considered when marked endocardial trabeculae at end-diastole exceeded a 2.3/1.0 ratio with respect to the compacted area. The diagnostic criteria for arrhythmogenic right ventricular dysplasia (4) and hypertrophic cardiomyopathy (5) were based on current consensus. Patient follow-up was performed to establish death, myocardial infarction, stroke, cardiac arrest, or hospitalization for life-threatening arrhythmias or need for radiofrequency ablation of any type of arrhythmia.

### Statistical analysis

Continuous variables with Gaussian distribution were expressed as mean  $\pm$  standard deviation and those with non-Gaussian distribution were expressed as median and interquartile range. Variables with normal distribution were compared using Student's t test and those with non-normal distribution with the Wilcoxon rank sum test. Categorical variables were compared using the chi-square test.

## RESULTS

Baseline characteristics of the 66 patients are shown in Table 1. Mean age was  $54.1 \pm 17.2$  years, 48.4% were men, and CRM mean ejection fraction was  $60.8 \pm 7.7$ %. The prevalence of various forms of FVA was: > 5000 VE in 77.2% of patients (n = 55), NSVT in 25.7% (n = 22), SVT in 6% (n = 4) and resuscitated cardiac arrest in 1.5% (n = 1). Cardiac MR detected significant abnormalities in 57% (n = 38) of patients. The most frequent pathologies were myocarditis (24%, n = 16), non-compacted myocardium (17%, n = 11) and LV systolic dysfunction (17%, n = 11). (Table 2). In patients with 24-hour Holter monitoring, the number of VE was higher in patients with abnormal CMR than in those with normal CMR (11887 vs. 8485, p = 0.049) (Figure 1). Figure 2 describes selected clinical case images.

### Clinical Events

In the mean follow-up of  $24 \pm 22$  months, the incidence of death, myocardial infarction, stroke, cardiac arrest, heart failure, hospitalization for serious arrhythmias or need for radiofrequency ablation was 6.06% (n = 4). Two patients had a new episode of VT requiring radiofrequency ablation, one patient developed polymorphic NSVT with hospitalization for antiarrhythmic treatment with flecainide and one patient had acute pulmonary edema. Patients who presented with events had a history of sustained VT in 2 cases and NSVT in the other two. None of the patients with frequent VE in the Holter monitoring presented clinical events at follow-up.

### DISCUSSION

This study showed structural heart disease in over 50% of patients with FVA and normal Doppler echocardiogram. The most frequent abnormalities detected in CMR were myocarditis, non-compacted myocardium and mild left ventricular dysfunction. This population of patients with ventricular arrhythmia and preserved systolic function has a low risk of cardiovascular events.

In patients with FVA it is necessary to assess cardiac risk. The clinical relevance of detecting underlying heart disease lies in the prognostic value presented by FVA in some cardiomyopathies and in treatment decision making, as for example use of implantable cardioverter defibrillator (ICD). Our work

shows that in FVA patients with usually normal or not conclusive complementary studies, contrast CMR reveals structural abnormalities in over 50% of cases. The CASPER registry published in 2009 evaluated patients with resuscitated cardiac arrest and normal baseline complementary studies including Doppler echocardiography. All patients underwent CMR with gadolinium along with other tests to expose channelopathies. The most common structural abnormality detected was arrhythmogenic ventricular dysplasia and myocarditis. Unlike the CASPER registry, our population was more heterogeneous, presenting resuscitated cardiac arrest only in one patient. However, the diagnostic yield was higher in our study (57% vs. 4.76% in the CASPER registry). This difference may be due to the high prevalence of channelopathies in the CASPER registry. (6) Sestito et al evaluated the ability of CMR without contrast to detect structural abnormalities in a pediatric population with monomorphic FVA and normal Doppler echocardiography. Among the 23 patients evaluated in this study, significant changes, mainly dysfunction and mild ventricular dilatation, were found in 77% of cases. (7) The association between FVA and structural abnormalities has a different clinical impact according to the type of heart disease. In ischemic cardiomyopathy, the presence of FVA in the era prior to beta-blockers was independently associated with increased morbidity and mortality. (8) Although some studies have failed to demonstrate the association between FVA and cardio-

Table 1. Baseline Characteristics

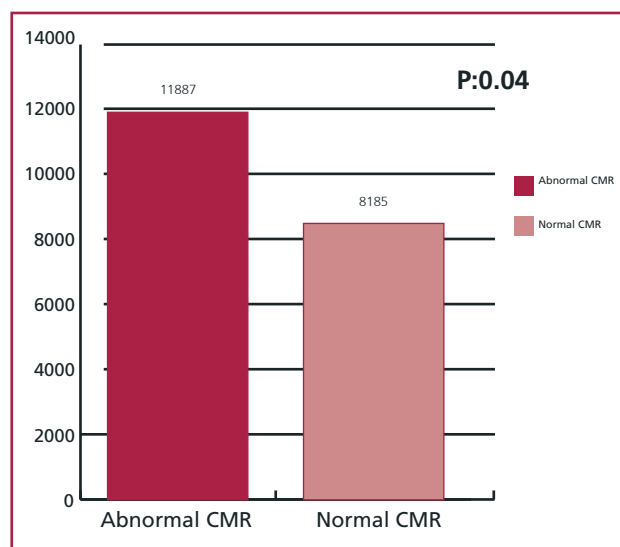
Baseline Characteristics	(n= 66)
Age (years), mean $\pm$ SD	54.1 $\pm$ 17.2
Men, % (n)	48.4 (32)
Hypertension, % (n)	33.3 (22)
Hypercholesterolemia % (n)	37.8 (25)
Diabetes, % (n)	7.5 (5)
Smoking, % (n)	4.5 (3)
<b>CMR volume and ejection fraction</b>	
LV ejection fraction (%), mean $\pm$ SD	60.8 $\pm$ .7.7
LV end-diastolic volume index (ml/m <sup>2</sup> ), mean $\pm$ SD	77.3 $\pm$ 18.6
LV end-systolic volume index (ml/m <sup>2</sup> ), mean $\pm$ SD	29.4 $\pm$ 11.3
LV mass index, (gr/m <sup>2</sup> ), mean $\pm$ SD	70.5 $\pm$ 16.5
RV ejection fraction (%), mean $\pm$ SD	56.0 $\pm$ .7.8
<b>Ventricular arrhythmia at study admission</b>	
N° of VE, median (25-75% percentile)	10697 (5618 - 13237)
24h ECG Holter monitoring > 5000 VE, % (n)	77.2 (51)
NSVT, % (n)	25.7 (17)
VT, % (n)	6.0 (4)
SD, % (n)	1.5 (1)

$\pm$  SD: Standard deviation. CMR: Cardiac magnetic resonance. LV: Left ventricular. RV: Right ventricular. VE: Ventricular extrasystoles. NSVT: Non-sustained ventricular tachycardia. VT: Ventricular tachycardia. SD: Sudden death.

**Table 2.** Types of abnormalities detected by cardiac magnetic resonance

Pathology	n (%)
Myocarditis	16 (24.2)
Non-compacted myocardium	11 (16.6)
LV systolic dysfunction	11 (16.6)
Myocardial infarction	7 (10.6)
LV hypertrophy	7 (10.6)
LV dilation	5 (7.5)
RV dilation	3 (4.5)
RV systolic dysfunction	1 (1.5)
Chagasic cardiomyopathy	1 (1.5)
Arrhythmogenic RV dysplasia	1 (1.5)

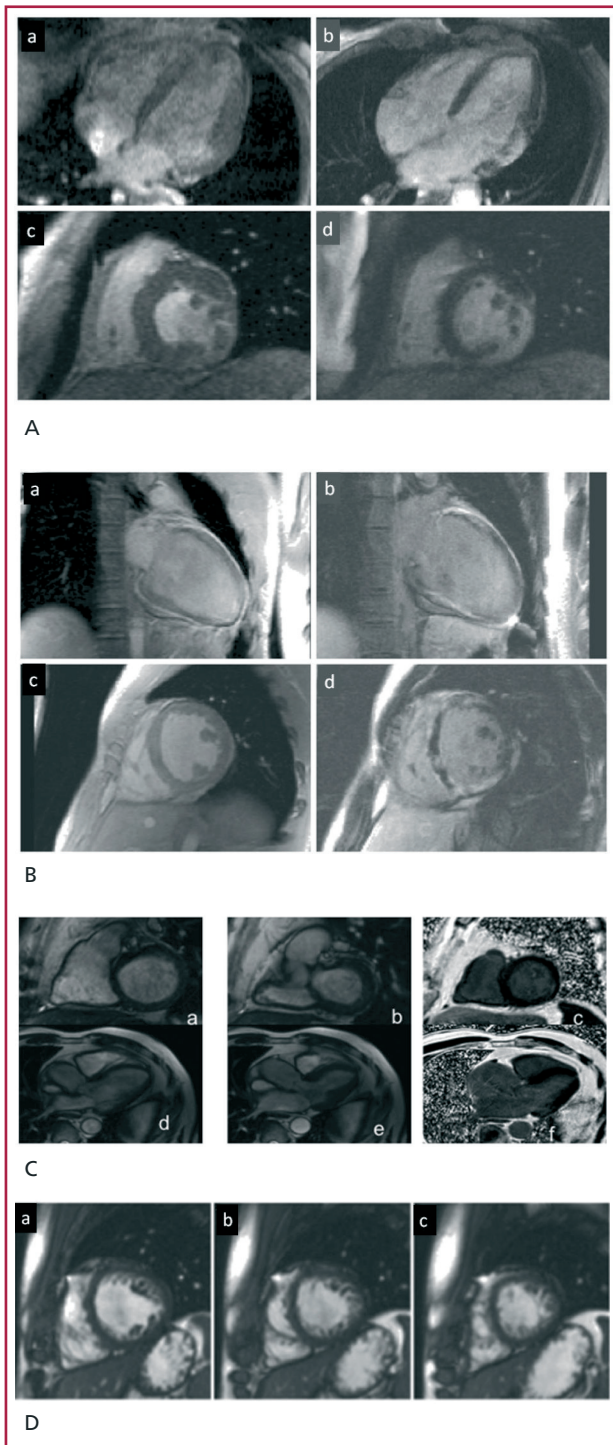
LV: Left ventricular. RV: Right ventricular



**Fig. 1.** Proportion of ventricular extrasystoles at baseline Holter monitoring according to the presence of cardiac magnetic resonance abnormalities. Bar graph showing the number of ventricular extrasystoles in patients with abnormal cardiac magnetic resonance (blue bar) and in patients with normal magnetic resonance (red bar)

vascular events in patients with previous infarction (9, 10), the recent ATRAMI study showed higher mortality in patients with NSVT after myocardial infarction. (11) Moreover, FVA could be an epiphenomenon of the ischemic myocardium. In diabetic subpopulations, the presence of silent ischemia and necrosis is more prevalent, and the detection of subendocardial infarct scar would allow more adequate patient treatment. (12) In this study, a previously unknown infarction scar was detected in 10.7% of patients. In patients with non-compacted myocardium and preserved LV systolic function, the presence of non-sustained FVA was not associated with increased mortality. (13-15) Nucifora et al evaluated the prevalence and extent of subendocardial DGE in 42 patients with non-compacted myocardium. Presence of DGE and its extension

was independently associated with a higher incidence of cardiovascular events and death. (16). In the study series, non-compacted myocardium was the second most common structural heart disease diagnosed. At present, CMR is considered the noninvasive technique of choice for the diagnosis of myocarditis without need for endomyocardial biopsy. (17). Regarding the sequel to myocarditis, its pathophysiology consists of necrotic tissue surrounded by heterogeneous tissue comprising healthy tissue mixed with injured cells, and at later stages by fibrosis that can be substrate for the development of reentrant ventricular tachycardia (VT). (18) In turn, VE is a known trigger for these arrhythmias. In a recent study published by Grün et al, presence of DGE in myocarditis patients significantly correlated with increased mortality at long-term follow-up, showing that it was the best predictor (HR 8.4,  $p < 0.001$ ). (19). In that study, none of the patients without LGE suffered from cardiac death. In this series, myocarditis was the most commonly diagnosed structural heart disease. In relation to arrhythmogenic right ventricular (RV) dysplasia, its detection is critical because the risk of cardiac arrest for reentrant VT is high, especially in the presence of FVA, justifying in many cases placement of an ICD. Its prompt detection at earlier stages allows closer monitoring to avoid the development of complications. In this study we identified a patient with arrhythmogenic RV dysplasia criteria. (20, 21) In the Aquaro et al study, the presence of RV abnormalities without arrhythmogenic RV dysplasia criteria was associated with increased long-term risk of cardiac death, appropriate ICD shocks or resuscitated cardiac arrest. (22). In our study 5.5% of patients presented with RV abnormalities without arrhythmogenic dysplasia criteria. Detection of incipient LV systolic dysfunction may correspond to an early stage of cardiomyopathy mediated by frequent VE or to idiopathic dilated cardiomyopathy. On the other hand, the presence of normal CMR in a FVA context with evidence of left bundle-branch block and inferior axis identifies a group of patients with RV or to a lesser extent LV outflow tract arrhythmia (23). These patients are at very low risk of adverse cardiac events. (24) The number of VE directly correlates with the risk of developing VE-mediated cardiomyopathy. The cutoff point to determine a population at high risk of developing cardiomyopathy is about 20000 VE; however, in many studies some cases can be detected at 10000 VE. (23-25) As in our study an increased number of VE was found in patients with abnormal CMR, the performance of CMR in patients with >10000 VE or repetitive phenomena might be considered. Absence of LGE and structural damage suggests VE-mediated cardiomyopathy. Reduced number of VE with treatment and improved systolic function at clinical follow-up confirm the diagnosis. In other cases of early stage idiopathic dilated cardiomyopathy, similar findings with ventricular dilatation and mild progressive ventricular dysfunction can be



**Fig. 2.** Selected clinical cases. **A.** Chagas Cardiomyopathy. Fifty-seven year-old female patient with a history of sustained ventricular tachycardia treated with amiodarone, sotalol and mexiletine. The 4-chamber long axis (**a**) and basal short axis (**b** and **c**) FLASH cine magnetic resonance images show left ventricular inferolateral wall thinning. Sequences for viability show late gadolinium enhancement in the left ventricular 4-chamber long-axis (**d**) and short axis (**e** and **f**) images. Late gadolinium enhancement highlights areas of myocardial fibrosis. **B.** Myocarditis. A 21 year-old male patient with a history of three syncope episodes and non-sustained ventricular tachycardia on Holter monitoring. Electrophysiological study was performed with induced sustained ventricular tachycardia. An implantable cardioverter defibrillator was indicated. In end-diastolic 2-chamber long axis (**a**) and basal short axis (**b**) FLASH cine magnetic resonance images, the patient presented with preserved left ventricular systolic function. Sequences to assess viability (**c** and **d**) show multiple late gadolinium enhancement foci with a predominantly epicardial pattern suggestive of myocarditis. **C.** Subendocardial infarction. A 68-year old male patient presenting palpitations and frequent ventricular arrhythmia in the ECG. In the true FISP cine imaging sequence, global left ventricular function is preserved. Left ventricular end-diastolic (**a**) and end-systolic (**b**) basal short axes are shown in the cine imaging. A small subendocardial enhancement is observed in inferobasal late gadolinium enhancement sequences (**c**). Left ventricular end-diastolic (**d**) and end-systolic (**e**) long axes are shown in the cine imaging. A small subendocardial enhancement is observed in the left ventricular inferolateral late gadolinium enhancement sequences (**f**). **D.** Non-compacted myocardium. A 35-year-old male patient with frequent ventricular arrhythmias. In the true-FISP cine magnetic resonance imaging prominent subendocardial trabeculae are observed in the mediolateral LV segment (**a** and **b**) and in the apical lateral segment (**c**). Mild systolic function impairment is observed.

segment involvement not detected by echocardiography (27). In the present series, LV hypertrophy was diagnosed in 10% of patients with CMR abnormalities. The future of CMR in the study of patients with FVA is not only limited to identify structural heart disease. Currently, CMR images are used to integrate them with those obtained by electroanatomic mapping to optimize the radiofrequency ablation strategy. (28, 29) There are few published studies that have evaluated the diagnostic value of CMR in patients with FVA without evidence of structural heart disease by Doppler echocardiography. In our country this is the first registry of patients with FVA and CMR.

The prognosis of patients with FVA and preserved systolic function is good and the incidence of cardiovascular events in an average two-year follow-up is low. An explanation for this finding could be that in structural abnormalities, systolic ventricular dysfunction is one of the highest risk predictors. None of the patients with frequent VE on Holter monitoring showed adverse events, whereas in patients with ventricular abnormalities, incidence of events was greater.

#### Limitations

The limitations of our study were the following: we conducted a retrospective analysis of clinical events

found at the clinical follow-up. (26) In our series, 17% of patients presented with mild LV dysfunction, 7% had mild LV dilatation, and 5% RV dilatation without LGE signs. CMR adequately determines epicardial and endocardial borders allowing accurate estimation of wall thickness, which is especially useful in the diagnosis of hypertrophic cardiomyopathy. In a recent study, CMR diagnosed 12% hypertrophic cardiomyopathy with apical, inferoseptal or basal anterolateral

through our electronic medical records. However, this system allows for a fairly accurate survey regarding admissions and relevant clinical events in patients whose follow-up was only performed at our hospital (55 patients). In turn, the retrospective nature and the small sample size did not allow us to draw conclusions regarding the prognostic value of CMR results for different events. However, the result of more than 50% structural abnormalities in patients with FVA indicates that CMR may be considered as another tool to study patients presenting a normal or inconclusive Doppler echocardiogram.

## CONCLUSIONS

In patients with FVA, the search for structural heart disease should not end in the presence of a normal Doppler echocardiogram. Structural damage diagnosed by CMR with gadolinium in patients with normal echocardiogram is greater than 50%. Patients with FVA on Holter monitoring, normal Doppler echocardiogram and minor CMR alterations present a low risk of cardiovascular events.

## RESUMEN

**Valor diagnóstico de la resonancia magnética cardíaca en pacientes con arritmia ventricular frecuente y ecocardiograma Doppler normal**

### Introducción

La arritmia ventricular frecuente puede ser una alteración eléctrica primaria o estar asociada con una cardiopatía. El impacto pronóstico y terapéutico depende de la presencia de cardiopatía estructural. El ecocardiograma Doppler torácico ha sido el estudio complementario más importante para evaluar la presencia de alteraciones estructurales cardíacas.

### Objetivos

Determinar la capacidad de la resonancia magnética cardíaca para detectar alteraciones estructurales a nivel cardíaco en pacientes con ecocardiograma Doppler normal y conocer la incidencia de eventos cardiovasculares adversos en el seguimiento.

### Material y métodos

Se incluyeron 66 pacientes consecutivos con arritmia ventricular frecuente definida como > 5.000 extrasístoles ventriculares en un registro Holter de 24 horas, taquicardia ventricular o muerte súbita resucitada con ecocardiograma Doppler normal. A todos los pacientes se les realizó una resonancia magnética cardíaca con protocolo para evaluar miocardiopatías.

### Resultados

El 57% de los pacientes presentaron alguna alteración estructural; las patologías diagnosticadas más prevalentes fueron la secuela de miocarditis, el miocardio no compactado y la secuela de infarto subendocárdico. En el seguimiento medio de  $24 \pm 22$  meses, la incidencia de eventos cardiovasculares adversos fue del 6,06%. El número de extrasístoles ventriculares fue mayor en los pacientes con resonancia anormal.

## Conclusiones

Este trabajo demuestra que en pacientes con arritmia ventricular frecuente con ecocardiograma Doppler normal la realización de una resonancia magnética cardíaca con gadolinio permite detectar en más de la mitad de los casos alguna alteración estructural. Los pacientes con arritmia ventricular frecuente en el Holter, Doppler normal y alteraciones leves en la resonancia presentan riesgo bajo de eventos cardiovasculares.

**Palabras clave** > Resonancia magnética cardíaca - Arritmias cardíacas - Cardiomiopatías

## Conflicts of interest

None declared.

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