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Original article

Myocardial Extracellular Volume Is not Associated With Malignant Ventricular Arrhythmias in High-risk Hypertrophic Cardiomyopathy

Jesús G. Mirelis,[a,b,c] Javier Sánchez-González,[a,d] Esther Zorio,[e] Tomas Ripoll-Vera,[f] Rafael Salguero-Bodes,[g] David Filgueiras-Rama,[a,b,h] Esther González-López,[a,b,c] María Gallego-Delgado,[a,b] Rodrigo Fernández-Jiménez,[a,b,i] María Jesús Soleto,[f] Juana Núñez,[f] Gonzalo Pizarro,[a,b,j] Javier Sanz,[i] Valentín Fuster,[a,i] Pablo García-Pavía,[a,b,c] and Borja Ibáñez[a,b,k,*]

[a] *Área de Fisiopatología del Miocardio, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Instituto de Salud Carlos III, Madrid, Spain*
[b] *CIBER de enfermedades CardioVasculares (CIBERCV), Spain*
[c] *Departamento de Cardiología, Hospital Universitario Puerta de Hierro, Majahonda, Madrid, Spain*
[d] *Departamento de Ciencia Clínica, Philips Healthcare, Spain*
[e] *Departamento de Cardiología, Hospital Universitario y Politécnico La Fe, Valencia, Spain*
[f] *Departamento de Cardiología, Hospital de Son Llâtzer & IdISPa, Palma de Mallorca, Spain*
[g] *Departamento de Cardiología, Hospital Universitario 12 de Octubre, Madrid, Spain*
[h] *Departamento de Cardiología, Hospital Universitario Clínico San Carlos, Madrid, Spain*
[i] *Department of Cardiology, The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, United States*
[j] *Departamento de Cardiología, Complejo Hospitalario Ruber Juan Bravo, Universidad Europea de Madrid, Madrid, Spain*
[k] *Departamento de Cardiología, IIS-Hospital Fundación Jiménez Díaz, Madrid, Spain*

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ABSTRACT

Introduction and objectives: Myocardial interstitial fibrosis, a hallmark of hypertrophic cardiomyopathy (HCM), has been proposed as an arrhythmic substrate. Fibrosis is associated with increased extracellular volume (ECV), which can be quantified by computed tomography (CT). We aimed to analyze the association between CT-determined ECV and malignant ventricular arrhythmias.

Methods: A retrospective case-control observational study was conducted in HCM patients with implantable cardioverter-defibrillator, undergoing a CT-protocol with continuous iodine contrast infusion to determine equilibrium ECV. Left ventricular septal and lateral CT-determined ECV was compared between prespecified cases (malignant arrhythmia any time before CT scan) and controls (no prior malignant arrhythmias) and among ECV tertiles.

Results: A total of 78 implantable cardioverter-defibrillator HCM patients were included; 24 were women, with a mean age of 52.1 ± 15.6 years. Mean ECV ± standard deviation in the septal left ventricular wall and was 29.8% ± 6.3% in cases (n = 24) vs 31.9% ± 8.5% in controls (n = 54); $P = .282$. Mean ECV in the lateral wall was 24.5% ± 6.8% in cases vs 28.2% ± 7.4% in controls; $P = .043$. On comparison of the entire population according to septal ECV tertiles, no significant differences were found in the number of patients receiving appropriate shocks. Conversely, we found a trend ($P = .056$) for a higher number of patients receiving appropriate shocks in the lateral ECV lowest tertile.

Conclusions: Extracellular volume was not increased in implantable cardioverter-defibrillator HCM patients with malignant ventricular arrhythmias vs those without arrhythmias. Our findings do not support the use of ECV (a surrogate of diffuse fibrosis) as a predictor of arrhythmias in high-risk HCM patients.

El volumen extracellular no se asocia a arritmias malignas en miocardiopatía hipertrófica de alto riesgo

Palabras clave:
Miocardiopatía hipertrófica
Tomografía computarizada
Volumen extracelular
Fibrosis difusa

RESUMEN

Introducción y objetivos: La fibrosis intersticial en miocardiopatía hipertrófica (MCH) se ha propuesto como substrato de arritmias malignas. La fibrosis se asocia a expansión del volumen extracelular (VEC) que se puede cuantificar por tomografía computarizada (TC). El objetivo es analizar la asociación entre VEC determinado por TC y la presencia de arritmias malignas.

* Corresponding author: Laboratorio Traslacional para la Imagen y Terapia Cardiovascular, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Instituto de Salud Carlos III, Melchor Fernández Almagro 3, 28029 Madrid, Spain.
E-mail address: bibanez@cnic.es (B. Ibáñez).

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Métodos: Estudio observacional de casos y controles en pacientes con MCH y desfibrilador automático implantable sometidos a TC con infusión continua de contraste yodado para cuantificar el VEC en equilibrio. Se comparó el VEC determinado por TC en las paredes septal y lateral de ventrículo izquierdo entre casos (presencia de arritmia maligna previa) y controles (sin arritmias malignas).

Resultados: Se incluyó a 78 pacientes con MCH-desfibrilador automático implantable, 24 eran mujeres con una edad media de 52,1 ± 15,6 años. El VEC medio ± desviación estándar en pared septal fue 29,8 ± 6,3% en casos (n = 24) frente a 31,9 ± 8,5% en controles (n = 54); p = 0,282. El VEC medio en pared lateral fue 24,5 ± 6,8% en casos frente a 28,2 ± 7,4% en controles; p = 0,043. No se encontraron diferencias en el número de pacientes con choques apropiados entre los diferentes terciles de VEC. Por el contrario, se encontró una tendencia (p = 0,056) de un mayor número de pacientes dentro del menor tercil de VEC en pared lateral con descargas apropiadas.

Conclusiones: El VEC en pacientes con MCH-desfibrilador automático implantable con arritmias malignas no se mostró incrementado comparado con pacientes con MCH-desfibrilador automático implantable sin arritmias. Estos hallazgos no apoyan en uso de VEC (subrogado de fibrosis difusa) como predictor de arritmias malignas en pacientes con MCH de alto riesgo.

Abbreviations

CMR: cardiac magnetic resonance
CT: computed tomography
ECV: extracellular volume
HCM: hypertrophic cardiomyopathy
ICD: implantable cardioverter-defibrillator
SCD: sudden cardiac death

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a genetically transmitted form of cardiomyopathy with an estimated prevalence of 1/500 inhabitants in the general population.[1–6] The disease can have a favorable outcome,[7] especially with contemporary management strategies[5]; however, sudden cardiac death (SCD) remains a risk, and estimation of SCD risk is a rapidly evolving field of research.

The main strategy used to prevent SCD in high-risk HCM patients is the insertion of an implantable cardioverter-defibrillator (ICD).[8–10] However, in most HCM patients the implanted ICD is never used. Furthermore, ICD insertion carries a risk of inappropriate shocks and other complications. There is therefore a need for better tools to stratify arrhythmia risk in HCM.

Ventricular arrhythmias leading to SCD in HCM are thought to develop from myocardial fibrosis.[11] Some studies have linked ventricular arrhythmias to focal fibrosis, assessed from the presence and extent of late gadolinium enhancement on cardiac magnetic resonance (CMR).[12–14] However, this relationship is not considered powerful enough to support ICD implantation as a primary prevention measure in American or European guidelines.[15,16] Late gadolinium enhancement-CMR does not detect diffuse fibrosis; however, postmortem histology shows that diffuse fibrosis is more prevalent after SCD in HCM patients than in deaths not linked to a cardiovascular cause or in aths in patients with left ventricular hypertrophy of hypertensive origin, suggesting that it is a proarrhythmic substrate.[11,17–20] To date, few studies have been designed to evaluate the association between malignant ventricular arrhythmias and diffuse fibrosis as detected noninvasively.[21,22]

Myocardial fibrosis is associated with increased extracellular volume (ECV), which can be quantified by CMR or computed tomography (CT).[23,24] The aim of our study was to determine whether quantification of ECV by CT, as a surrogate measure of diffuse fibrosis, could distinguish between the presence or absence of malignant ventricular arrhythmias in HCM patients fitted with an ICD (ICD-HCM patients).

METHODS

A retrospective case-control observational study was performed in ICD-HCM patients. Between November 2013 and February 2015, 78 ICD-HCM patients (> 18 years old without contraindications for contrast CT) were recruited at 5 Spanish cardiomyopathy units (*Puerta de Hierro-Majadahonda*, Madrid, n = 24; *La Fe*, Valencia, n = 15; *Son Llatzer*, Palma de Mallorca, n = 17; *Clínico San Carlos*, Madrid, n = 10; *12 de Octubre*, Madrid, n = 12). The study was approved by the local ethics committees. All patients had been previously implanted with an ICD according to current risk stratification guidelines.[16,25,26] All patients gave written informed consent.

Case/Control Prespecified Groups

Cases consisted of HCM patients with an ICD implanted for secondary prevention or those with an ICD implanted for primary prevention and receiving documented appropriate ICD therapy (antitachycardia pacing or shock). Control patients were defined as HCM patients with an ICD implanted for primary prevention but with no history of ICD therapy at the time of enrolment.

Computed Tomography Protocol

Extracellular volume was quantified through CT data acquired with 2 CT scanners: an ICT 256 (Philips, Best, The Netherlands) at the *Centro Nacional de Investigaciones Cardiovasculares* (CNIC), Madrid (n = 61 participants) and a Lightspeed VCT 64 Slice CT scanner (General Electric, United States) at Son Llatzer Hospital, Mallorca (n = 17 participants). Before CT scanning, patients underwent tests to verify heart rate, blood pressure, and cardiac rhythm (sinus rhythm, atrial fibrillation, or pacemaker), and blood was drawn for a hematocrit test. The CT imaging protocol consisted of scout sequences and 2 acquisitions (precontrast and postcontrast) with coverage in the z direction of 160 mm (to provide maximum coverage of the left ventricle). Computed tomography data were acquired prospectively at 70% of the RR interval. Postcontrast acquisitions were performed 25 minutes after initiation of infusion with iodinated contrast agent (Omnipaque 300 mg L/mL, GE Healthcare). The contrast was infused rapidly with a CT injector (Medrad Stellant for scans at the CNIC; Ulrich Medical missouri for scans at Son Llatzer Hospital) at a rate of 3 mL/s to a total volume of 1 mL/kg. Upon completion of the rapid infusion, continuous perfusion was initiated with an infusion pump at 1.88 mL/h/kg and continued for 25 minutes (Hospira PlumA+ at the CNIC; Braun Space Infusomat at Son Llatzer Hospital).[24] For safety reasons, the maximum volume of administered contrast

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