

## Importance of Sudden Cardiac Death Risk Stratification in Hypertrophic Cardiomyopathy. Response



### La importancia de la estratificación de riesgo de muerte súbita en la miocardiopatía hipertrófica. Respuesta

#### To the Editor,

We are grateful for the comments of Martínez-Moreno et al in relation to our work on the results of implantable cardioverter-defibrillator (ICD) implantation in hypertrophic cardiomyopathy.<sup>1</sup> Whilst it is true that our study was a small series with a relatively short follow-up, we believe that it was representative of the hypertrophic cardiomyopathy population in nonspecialized centers. This nonspecialization would explain the low rate of appropriate therapies compared with that in previous studies, which are from large specialized centers attending patients with the most severe disease. The authors' observations are appropriate, given the recent publication of the new European Society of Cardiology guidelines on hypertrophic cardiomyopathy,<sup>2</sup> which recommend the use of HCM Risk-SCD,<sup>3</sup> a new tool for evaluating sudden cardiac death risk, which naturally was not used in our cohort when the decision was made on ICD implantation. We calculated this risk a posteriori in the 48 primary prevention patients from our cohort, with the following results: 12 patients (25%) would have had a calculated risk of < 4%, and therefore no indication for ICD implantation according to the new guidelines; 7 patients (14.6%) would have had a risk of between 4% and 6% (class IIb ICD indication), and 29 patients (60.4%) would have had a risk > 6% (class IIa indication). Interestingly, the 3 patients in our cohort who received appropriate therapies would have had a risk of > 6%. Had we applied the new guidelines to our cohort, we would have "saved" ICD implantation in 39.6% of the patients, who, in addition, had received no shocks at the time of follow-up. Also, as noted in the original article, secondary prevention patients have a paradoxically low risk profile, and although HCM Risk-SCD is not valid for secondary prevention, in which ICD implantation has a class I indication, we calculated the risk for our cohort patients, using the data available. All patients would have had a theoretical risk of < 6%, and consequently would have had no indication for ICD prior to their episode of ventricular arrhythmia. We agree that HCM Risk-SCD improves patient selection in those with 1 or more risk factors, but it does not solve the problem that many sudden

cardiac deaths occur in patients who are theoretically low risk, and so cannot be identified using tools based on classic risk factors. It surprises us that, in the development of HCM Risk-SCD, there was no evaluation of imaging (such as fibrosis on magnetic resonance<sup>4</sup>), electrophysiological,<sup>5</sup> or genetic parameters,<sup>6</sup> which could help to better identify at risk patients in the future.

Axel Sarrias,<sup>a,\*</sup> Enrique Galve,<sup>b</sup> Xavier Sabaté,<sup>c</sup> and Roger Villuendas<sup>a</sup>

<sup>a</sup>Servicio de Cardiología, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain

<sup>b</sup>Servicio de Cardiología, Hospital Universitari Vall d'Hebron, Barcelona, Spain

<sup>c</sup>Servicio de Cardiología, Hospital Universitari de Bellvitge, L'Hospitalet del Llobregat, Barcelona, Spain

\* Corresponding author:

E-mail address: [axelsarrias@gmail.com](mailto:axelsarrias@gmail.com) (A. Sarrias).

Available online 20 April 2015

## REFERENCES

1. Sarrias A, Galve E, Sabaté X, Moya A, Anguera I, Nuñez E, et al. Terapia con desfibrilador automático implantable en la miocardiopatía hipertrófica: utilidad en prevención primaria y secundaria. Rev Esp Cardiol. 2014 [Epub ahead of print]. Available at: <http://dx.doi.org/10.1016/j.recresp.2014.05.024>
2. Elliott PM, Anastakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al. ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy. Eur Heart J. 2014;35:2733-79.
3. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastakis A, Rapezzi C, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). Eur Heart J. 2014;35:2010-20.
4. Chan RH, Maron BJ, Olivetto I, Pencina MJ, Assenza GE, Haas T, et al. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. Circulation. 2014;130:484-95.
5. Kang KW, Janardhan AH, Jung KT, Lee HS, Lee MH, Hwang HJ. Fragmented QRS as a candidate marker for high-risk assessment in hypertrophic cardiomyopathy. Heart Rhythm. 2014;11:1433-40.
6. Zhang L, Mmagu O, Liu L, Li D, Fan Y, Baranchuk A, et al. Hypertrophic cardiomyopathy: Can the noninvasive diagnostic testing identify high risk patients? World J Cardiol. 2014;6:764-70.

SEE RELATED ARTICLE:

<http://dx.doi.org/10.1016/j.rec.2015.01.004>

<http://dx.doi.org/10.1016/j.rec.2015.02.007>

## Sensitivity and Negative Predictive Value of Treadmill Exercise Stress Testing for the Diagnosis of Catecholaminergic Polymorphic Ventricular Tachycardia



### Sensibilidad y valor predictivo negativo de la ergometría para el diagnóstico de la taquicardia ventricular polimórfica catecolaminérgica

#### To the Editor,

We read with interest the article<sup>1</sup> and scientific letter<sup>2</sup> published by Domingo et al in *Revista Española de Cardiología*, and would like to congratulate the authors for their work demonstrating the pathogenicity of the RyR2<sup>R420Q</sup> mutation as the cause of catecholaminergic polymorphic ventricular tachycardia (CPVT), as well as the description of individuals with the RyR2 C2277R mutation. These are 2 important contributions to our knowledge about this disease.

However, we would like to mention a series of considerations concerning the diagnosis of CPVT, the criteria used, the details of

the diagnostic protocol used by the authors and, singularly, the extraordinary diagnostic yield of the exercise stress test (performed on a treadmill according to the Bruce protocol).

The exercise stress test is considered to be the most important and most widely recommended diagnostic test for CPVT,<sup>3</sup> but it is not reproducible and the results can be negative<sup>4</sup> in individuals with the disease. In the context of family screening, the recommendation of international experts representing Europe, the United States, and the Asia-Pacific region is that the observation of ventricular premature beats is sufficient for the test to be considered positive.<sup>5</sup>

The fact is that diagnostic sensitivity is highly problematic in this disease. Up to 30% of the patients in published series who experienced sudden cardiac death had been asymptomatic until that time, and events have been reported in individuals with a negative baseline exercise stress test.<sup>6</sup> Moreover, the sensitivity of the exercise stress test is too low (13%-56% in carriers of RyR2 mutations).<sup>7</sup>

The diagnostic criteria are not completely defined. Initial requirements were the documentation of polymorphic or bidirectional ventricular tachycardias or ventricular fibrillation

during exercise stress testing or following catecholamine infusion.<sup>8</sup> Recently, there have been reports of the use of diagnostic thresholds such as more than 10 premature ventricular contractions/minute,<sup>7</sup> bigeminy,<sup>6</sup> or couplets as the “minimum” ventricular arrhythmia, whose presence is indicative of a diagnosis of CPVT. In addition, although catecholamine infusion is not a totally reliable test, it continues to be used to enhance sensitivity in the diagnosis of this disease, especially when dealing with an index case. However, recent studies have reported the limited usefulness of catecholamine infusion because of its very low sensitivity (28%)<sup>7,9</sup> and specificity<sup>9</sup> for the diagnosis of CPVT. In one study, it was positive in 56 patients with a negative exercise stress test.<sup>7</sup>

The reality is that the available tests are insufficiently sensitive, and their negative predictive value is much lower than desired. However, the articles referred to in this letter reports results in terms of sensitivity (89%) and negative predictive value (93%) that do not agree with those reported to date, and convey the message that a negative exercise stress test rules out CPVT. These data probably require an in-depth study of a larger number of members of the family in question and, of course, cannot be extrapolated to other populations with other mutations in what, in our opinion, constitutes a selection bias.

In accordance with the recommendation of the scientific societies,<sup>5</sup> a negative exercise stress test does not rule out CPVT. The disease can be confirmed by the presence of specific ventricular arrhythmias during exercise but, in the context of family screening, just 1 premature ventricular contraction is enough to render the results of the test abnormal, and probably justifies the introduction of preventive treatment with beta-blocker therapy. Moreover, the use of catecholamine infusion should be restricted to selected cases, and should not be included in the protocol to be applied on a general basis.

Pablo M. Ruiz Hernández\* and Fernando Wangüemert Pérez

Área de Cardiopatías Familiares, Cardiant, Centro Médico Cardiológico, Las Palmas de Gran Canaria, Spain

\*Corresponding author:

E-mail address: [pabloruizher@secardiologia.es](mailto:pabloruizher@secardiologia.es)

(P.M. Ruiz Hernández).

Available online 20 April 2015

## REFERENCES

- Domingo D, Neco P, Fernández-Pons E, Zissimopoulos S, Molina P, Olagüe J, et al. Rasgos no ventriculares, clínicos y funcionales de la mutación RyR2<sup>R420Q</sup> causante de taquicardia ventricular polimórfica catecolaminérgica. *Rev Esp Cardiol.* 2015;68:398–407.
- Domingo D, López-Vilella R, Arnau MÁ, Cano Ó, Fernández-Pons E, Zorio E. Una nueva mutación en el gen del receptor de la rianodina (RyR2 C2277R) como causa de taquicardia ventricular polimórfica catecolaminérgica. *Rev Esp Cardiol.* 2015;68:71–3.
- Leenhardt A, Denjoy I, Guicheney P. Catecholaminergic polymorphic ventricular tachycardia. *Circ Arrhythm Electrophysiol.* 2012;5:1044–52.
- Hayashi M, Denjoy I, Extramiana F, Maltret A, Buisson NR, Lupoglazoff JM, et al. Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia. *Circulation.* 2009;119:2426–34.
- Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm.* 2013;10:1932–63.
- Hayashi M, Denjoy I, Hayashi M, Extramiana F, Maltret A, Roux-Buisson N, et al. The role of stress test for predicting genetic mutations and future cardiac events in asymptomatic relatives of catecholaminergic polymorphic ventricular tachycardia probands. *Europace.* 2012;14:1344–51.
- Marjamaa A, Hiiippala A, Arrhenius B, Lahtinen AM, Kontula K, Toivonen L, et al. Intravenous epinephrine infusion test in diagnosis of catecholaminergic polymorphic ventricular tachycardia. *J Cardiovasc Electrophysiol.* 2012;23:194–9.
- Priori SG, Napolitano C, Memmi M, Colombi B, Drago F, Gasparini M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation.* 2002;106:69–74.
- Krahn AD, Healey JS, Chauhan VS, Birnie DH, Champagne J, Sanatani S, et al. Epinephrine infusion in the evaluation of unexplained cardiac arrest and familial sudden death: from the cardiac arrest survivors with preserved ejection fraction registry. *Circ Arrhythm Electrophysiol.* 2012;5:933–40.

### SEE RELATED ARTICLES:

<http://dx.doi.org/10.1016/j.rec.2014.04.023>

<http://dx.doi.org/10.1016/j.rec.2014.07.022>

<http://dx.doi.org/10.1016/j.rec.2015.02.011>

<http://dx.doi.org/10.1016/j.rec.2015.02.006>

## Sensitivity and Negative Predictive Value of Treadmill Exercise Stress Testing for the Diagnosis of Catecholaminergic Polymorphic Ventricular Tachycardia. Response



### Sensibilidad y valor predictivo negativo de la ergometría para el diagnóstico de la taquicardia ventricular polimórfica catecolaminérgica. Respuesta

#### To the Editor,

We wish to thank Ruiz Hernández and Wangüemert Pérez for their interest in our articles.<sup>1,2</sup>

We used diagnostic criteria that were accepted at that time. With the recent consensus,<sup>3</sup> doubts remain only about II:9, which requires the presence of *ventricular premature beats* or *bidirectional ventricular tachycardia* in relatives during the exercise stress test (EST).<sup>3</sup> Other authors require *frequent* isolated ventricular premature beats.<sup>4</sup> A family member, especially if older than 40 years, can have a few ventricular premature beats, despite having a negative genotype. Thus, the minimum number of ventricular premature beats is imprecise and two isolated premature beats appear to be insufficient to make a diagnosis of such importance for patients and their descendants.

The yield of EST varies (ranging from the 25% reported by Ruiz Hernández and Wangüemert Pérez to 100%),<sup>5</sup> and perhaps depends on the point at which the mutation occurs. We had no intention of conveying the idea that a negative EST rules out the disease.<sup>1,2</sup> A conclusive genetic study supports a positive EST and identifies carriers with a negative EST. In its absence, we perform Holter monitoring and an epinephrine test in relatives with a negative EST (not included in the consensus statement),<sup>3</sup> and if they test negative, these individuals undergo follow-up with periodic EST. There are no studies on the value of epinephrine challenge in family members, but its usefulness has been documented in probands (which is included)<sup>3</sup> and in families with cardiac arrest with preserved left ventricular ejection fraction<sup>6</sup> and may justify its performance in the present context.

## FUNDING

Instituto de Salud Carlos III, Spain, and the ERDF (PI14/01477, RD12/0042/0029, European Union, European Regional Development Fund, “A way of making Europe”); *Prometeo* 2011/027, Spanish Society of Cardiology (grant awarded to Pedro Zarco); and the *Agence Nationale de la Recherche* (ANR-13-BSV1-0023-03).