



## EDITORIAL COMMENT

# A new look into hypertrophic cardiomyopathy based on clinical evidence



## Uma nova análise à miocardiopatia hipertrófica baseada na evidência clínica

Gláucia Maria Moraes de Oliveira

*Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil*

Hypertrophic cardiomyopathy (HCM) was first described by Donald Teare et al. in 1957 in a series of eight patients with asymmetric septal hypertrophy.<sup>1</sup> Later in that decade, Morrow and Braunwald described three cases of a clinical syndrome mimicking aortic stenosis, which was solved by resection of the subaortic interventricular septum.<sup>2</sup>

HCM has been reported in several countries, in individuals of both sexes with varied racial and ethnic backgrounds, with or without resting left ventricular obstruction, but with similar genotypic abnormalities. Its estimated incidence is 1 per 500 individuals in the general population (0.2%), but delay in diagnosis is common. HCM is an important public health problem due to sudden cardiac death (SCD), heart failure (HF), atrial fibrillation and ventricular arrhythmias that occur in the course of the disease.<sup>3</sup>

HCM is a monogenic disease caused by a mutation in one of the 13 or more genes encoding the protein components of the sarcomere. It has an autosomal dominant inheritance pattern and a high degree of phenotypic heterogeneity. The most frequent mutations are in the genes encoding myosin heavy chain 7 (*MYH7*), myosin-binding protein C (*MYBPC3*) and cardiac troponin T (*TNNT2* and *TNNI3*), with familial occurrence of approximately 60%.<sup>4</sup> Use of modern diagnostic methods, such as exercise echocardiography, cardiovascu-

lar magnetic resonance imaging and genetic testing, as well as invasive treatments for the obstructive forms and implantable cardioverter-defibrillators (ICDs) for ventricular arrhythmias, mean that long-term mortality in the general population with HCM is low.<sup>5</sup>

The Italian Registry for Hypertrophic Cardiomyopathy enrolled 1677 HCM patients from 40 institutions, mostly referral centers, from May 2000 to May 2002. Most patients were male (62%), in their fourth to sixth decade of life, and had few symptoms (89% in New York Heart Association [NYHA] functional class I/II). Family screening was performed in 40% and resting left ventricular obstruction was observed in 25% of the patients. The mean follow-up period was 9.7 years, with cardiovascular mortality of 1%/year, predominantly due to HF, followed by SCD (0.4%/year). Few patients received an ICD (4%) or invasive treatment for obstructive forms (14%), and fewer than 1% underwent genetic testing.<sup>6</sup>

The Portuguese Pro-HCM Registry enrolled 1042 HCM patients from 29 institutions, mostly non-referral centers, from April 2013 to April 2015. Most patients were male (59%); mean age at diagnosis was 53±16 years and 27% were older than 65 years, and few had symptoms (90% in NYHA class I/II). Family screening was performed in 33% and resting left ventricular obstruction was observed in 35% of the patients. The mean follow-up period was 3.3 years, with cardiovascular mortality of 0.65%/year, predominantly due to HF (0.25%/year), followed by SCD (0.22%/year) and stroke-related death (0.04%/year). Approximately 13% of

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E-mail address: [glauciamoraesoliveira@gmail.com](mailto:glauciamoraesoliveira@gmail.com)

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the patients received an ICD, and 13% underwent invasive treatment for the obstructive forms. Genetic testing was performed in 51% of the patients.<sup>7</sup>

The Pediatric Cardiomyopathy Registry enrolled 1085 HCM patients under the age of 18 years, from 98 centers in the US and Canada, from January 1990 to February 2009. Of these, 788 children had isolated HCM, with relatively normal height and weight. Most patients were male (68%); mean age at diagnosis was 6.0±6.3 years, and few presented with congestive HF (15%). Children diagnosed with HCM at the age of one year or older had a death or heart transplantation rate of 3% (95% confidence interval 1-5%) at the age of two years.<sup>8</sup>

These two registries in adult patients,<sup>6,7</sup> more than a decade apart, and the pediatric registry<sup>8</sup> show some divergences from the HCM management recommended in the guidelines.<sup>9,10</sup> The most important difference is that patients with younger age at disease onset, a positive family history and positive gene testing are likely to have more severe disease and are at higher risk for non-SCD and SCD, and may thus benefit more from early and accurate risk stratification. It is worth noting that left ventricular outflow tract obstruction, left ventricular systolic dysfunction, and HF have been reported to be risk factors for non-SCD in children and adults.<sup>4,6-8</sup>

The risk factors for SCD indicating the need for primary prevention with an ICD are older age, family history of HCM-related SCD, unexplained recent syncope, massive left ventricular hypertrophy, multiple bursts of non-sustained ventricular tachycardia on ambulatory electrocardiography, left atrial diameter, left ventricular outflow gradient, and hypotension or attenuated blood pressure response to exercise.<sup>9,10</sup> In addition, most HCM patients will not have SCD, and events still occur in those with no risk factors or considered at low risk. On the other hand, ICD use for primary prevention based on these risk factors has been associated with an appropriate therapy rate of 17% and inappropriate shocks in 27% of patients during a five-year follow-up.<sup>11</sup>

It is quite clear that different clinical courses represent a heterogeneous spectrum of HCM, reflecting different pathophysiologies, and requiring improvement in risk stratification for younger individuals and adults. Cardiovascular magnetic resonance imaging is a novel tool to improve risk stratification based on the detection of myocardial fibrosis, using late gadolinium enhancement to identify an arrhythmogenic substrate.<sup>11</sup>

Based on these data, the US National Heart Lung and Blood Institute sponsored an international registry with 2750 HCM patients at 41 sites, to assess the disease's natural history and to address limitations in the available evidence to improve prognostication in HCM. This study suggested that, unlike what is stated in the guidelines, most HCM patients are asymptomatic and have a good prognosis. It was aimed not only at proving this hypothesis, but at stratifying the small subset of HCM patients who experience serious consequences, such as SCD, or who progress to refractory HF.<sup>11</sup>

Registries such as Pro-HCM<sup>7</sup> provide important information on different aspects of the management of HCM. The Pro-HCM registry showed that overall mortality in older patients, followed in non-referral centers, who needed few procedures to treat obstructive forms or for primary

prevention of SCD, was similar (1.9%/year) to that of the general Portuguese population (1.1%/year).

Non-familial HCM, characterized by a negative family history and no sarcomere mutations, has recently been described as being a lower-risk form of the disease, with later onset and less severe clinical course, which may explain the results observed in the Italian and Portuguese registries. Non-familial HCM patients are more likely to be male and older, and to have non-asymmetric hypertrophy and coexistent hypertension.<sup>12</sup> It is probable that the pro-fibrotic state, myocardial injury and wall stress resulting from a sarcomere mutation influence collagen metabolism, affecting myocardial hemodynamics and remodeling, which may lead to a poor prognosis.<sup>12</sup>

Finally, the results of registries and findings on the subgroup of non-familial HCM will have important implications for the clinical management of HCM patients, and will probably lead to modifications in the guidelines in the near future.

## Conflicts of interest

The author has no conflicts of interest to declare.

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