



## EDITORIAL COMMENT

# Predicting risk of sudden death in hypertrophic cardiomyopathy: Can additional simple markers help?



## Previsão de risco de morte súbita na miocardiopatia hipertrófica: poderão marcadores simples adicionais constituir uma ajuda?

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Available online 16 March 2017

Hypertrophic cardiomyopathy (HCM) is a common genetic cardiovascular disorder, of which sudden cardiac death (SCD) is the most feared potential manifestation. Risk stratification for SCD has always been one of the greatest challenges in the management of the disease.

Malignant ventricular arrhythmias are possibly the most common cause of SCD in HCM, although there are other potential causes, and in fact the pathophysiologic mechanisms leading to syncope and SCD in HCM are not completely understood. Myocyte disarray, cardiac hypertrophy, small-vessel coronary artery disease, and increased interstitial fibrosis are consistently found in the disease,<sup>1</sup> and unquestionably play a role in the risk of SCD, although possibly to different and varying degrees in individual patients, depending also on the underlying genetic sarcomere alteration and tempered by additional genetic and external factors. The disease substrate contributes to functional endothelial and myocardial impairment, malignant arrhythmias, myocardial remodeling, and autonomic dysfunction, all of which can trigger sudden death under the appropriate circumstances.

Translated into the clinical scenario, non-sustained ventricular tachycardia episodes, unexplained non-vasovagal syncope (particularly in young patients), abnormal blood pressure response to exercise, left ventricular outflow obstruction, degree of hypertrophy, and progression to chamber dilatation, are some of the known identifiable potential risk factors for the occurrence of SCD. Several of these clinical signs are included in the prognostic index currently recommended for application to HCM patients,<sup>2</sup> a risk prediction model that estimates individual five-year risk of SCD. Age at diagnosis and a family history of sudden death are other risk factors incorporated in the model. The strategy currently used, although validated,<sup>3</sup> is not without its critics.<sup>4</sup> In fact, in such a complex disease, there will never be a perfect strategy to accurately predict the risk of SCD.

Besides clinical and imaging-derived risk factors, an ideal biomarker for risk stratification in HCM would be one that could easily, accurately and cost-effectively help identify HCM patients at higher risk for cardiovascular events (including SCD), and would be better than or at least additive to already identified biomarkers for determining prognosis and in decision-making processes.

Several biomarkers – considered here in a strict sense as biochemical molecules – have been studied in HCM, including some involved in inflammatory, hypertrophic and

DOI of original article:

<http://dx.doi.org/10.1016/j.repc.2016.09.014>

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<http://dx.doi.org/10.1016/j.repc.2017.02.005>

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fibrosis signaling pathways.<sup>5,6</sup> However, only natriuretic peptides (NPs) – wall stress markers – have been reproducibly associated with symptoms of heart failure, severity of hypertrophy, cardiac remodeling and imaging signs of left ventricular dysfunction.<sup>5–7</sup> High levels of NPs are also associated with the presence of fibrosis in cardiac magnetic resonance imaging of patients with symptomatic ventricular arrhythmias. However, although the utility of late gadolinium enhancement for detecting myocardial fibrosis is well established, current data do not support its use in prediction of SCD risk.<sup>2,8</sup> Regarding prognosis, plasma NP levels are independent predictors of morbidity and mortality, particularly with regard to heart failure-related events, but not to SCD.<sup>9–11</sup>

Inflammation plays a central role in the pathogenesis of many clinical conditions. Interleukin-6 (IL-6) and tumor necrosis factor (TNF- $\alpha$ ) are the inflammatory biomarkers most studied in HCM patients. IL-6, a pro-inflammatory cytokine that regulates leukocyte activity, is secreted by all the nucleated cells of the heart and also by skeletal muscle. Its levels are elevated in HCM patients, although no correlation with left ventricular hypertrophy or function has been found.<sup>5,12,13</sup> TNF- $\alpha$  (cachexin), a cytokine involved in systemic inflammation whose levels are generally found to be increased in HCM,<sup>5</sup> is produced not only by activated macrophages but also by many other cell types. Its primary role is in the regulation of immune cells. It has diverse actions on various organ systems, generally together with interleukin-1 and IL-6. Both biomarkers (TNF- $\alpha$  and IL-6) may promote the development of cardiac hypertrophy and fibrosis, through the activation of matrix metalloproteinases and their tissue inhibitors, and may have a role in the pathogenesis of HCM, although by as yet unidentified mechanisms.<sup>5,12,13</sup>

In the study by Ozyilmaz et al. published in this issue of the *Journal*,<sup>21</sup> the authors studied another marker of inflammation, the neutrophil-to-lymphocyte ratio (NLR), in a population of 97 patients with HCM followed for three years, and analyzed the association of NLR with prognosis. They found higher NLR in patients than in controls, and higher NLR values were identified in patients with fragmented QRS, ventricular tachycardia, pre-syncope, longer QTc interval (>440 ms), and >6% predicted five-year risk of SCD. Correlation was found only between QTc duration and NLR.

The authors linked higher NLR values to high-risk patients (with a worse prognosis regarding ventricular arrhythmic events), indicating a possible need for closer monitoring for ventricular arrhythmias in patients with high NLR.

NLR can be altered in diverse clinical conditions and may predict cardiovascular mortality,<sup>14</sup> and has emerged as a strong marker of an adverse prognosis, including in acute coronary syndromes<sup>15–18</sup> and in acute decompensated heart failure.<sup>19</sup> In fact NLR may be a predictor of mortality in all conditions,<sup>20</sup> since it is potentially affected in a large number of diverse situations, including hypertension, diabetes mellitus, heart disease, thyroid, renal and hepatic dysfunction, cancer, local or systemic infection, inflammatory disease, and medication with various drugs.<sup>20</sup> It should be noted that some (but not all) of these conditions were excluded from the study by Ozyilmaz et al.<sup>21</sup> It may not always be possible to exclude all potential confounders, because a 'pure' middle-aged HCM population probably

does not exist. However, the effects of the aforementioned potential confounders on NLR levels should be taken into account when assessing the application of a new biomarker of SCD risk in HCM that may impact on the decision whether to implant an implantable cardioverter-defibrillator.

The role of chronic inflammation and reparative fibrosis predisposing to ventricular (and possibly atrial) arrhythmias and remodeling in HCM is yet to be demonstrated. It is not known whether inflammation and cardiac repair (fibrosis) in the disease is actually responsible for both increased NLR values and QRS prolongation, which would explain the association found by Ozyilmaz et al.<sup>21</sup> Furthermore, genetic characterization is an important marker of HCM, and it would be interesting to assess in future studies whether different genetic populations with HCM – associated with mutations in the same or different sarcomere genes – behave similarly or differently regarding NLR values.

It is possible that as a marker of prognosis – or index of frailty? – in many situations, NLR, although non-specific, may be also useful in HCM, and the work by Ozyilmaz et al. encourages us to keep an open mind regarding new possibilities of risk stratification in HCM.

## Conflicts of interest

The author has no conflicts of interest to declare.

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