

Cutting through the Fat: Relationship Between Comorbidities and Arrhythmias in Hypertrophic Cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is a commonly encountered inherited heart disease with an estimated prevalence of 1:200 to 1:500¹. Approximately 30-40% of those patients diagnosed with HCM will experience adverse events (sudden cardiac death [SCD], heart failure, atrial fibrillation). Risk stratification for arrhythmias in HCM has been typically based upon five traditional noninvasive pillars (syncope, left ventricular hypertrophy >30mm, non-sustained VT, family history of sudden cardiac death, and abnormal blood pressure response to exercise). There has been some evolution in our understanding of risk, with the demotion of some to risk modifiers and identification of new risk markers/predictive scoring strategies (LGE on CMR, apical aneurysms, EF <50%). In HCM patients, comorbidities (obesity, hypertension, obstructive sleep apnea) have been identified as significant modifiers of disease penetrance, severity, and clinical course, particularly in relation to symptoms and heart failure²⁻⁴. The relationship of comorbidities to arrhythmias is less explored, but population-level data in non-HCM patients suggests that comorbidities can influence arrhythmia risk^{5,6}. Therefore, in HCM patients, if there were a positive association, this would provide an additional tool to refine arrhythmia risk.

In this issue of the *Journal of Cardiovascular Electrophysiology*, Sridharan et al.⁷ explore and attempt to answer this important question - what is the association of comorbidities in HCM patients with arrhythmia risk? This paper studies a large cohort of 2269 patients of >18 years evaluated between 2004 and 2018.

The mean age was 54 ± 15 years, with 1392 (61%) male, and a follow-up average of 4.0 ± 3.4 years. 1702 (75%) had [?]1 medical comorbidity, and 50% of patients had [?]2 comorbidities, most commonly obesity (43%), hyperlipidemia (39%), and hypertension (27%). 198 (11%) HCM patients developed new-onset AF over follow-up at a rate of 2.6% per year. On univariate analysis, obesity was associated with a 1.7-fold increase in risk for AF development compared to patients with normal BMI (95% CI 1.0, 2.7, $p=0.03$). In addition, 12% of obese patients developed AF (rate of 3.3%/year) compared to just 7% with normal BMI (rate of 1.6%/year; $p=0.006$). No other comorbidities were significant by univariate analysis. However, importantly on multivariate analysis, obesity did not show an association with AF (OR 1.3 [95% CI 0.95, 1.79, $p=0.10$). Concerning SCD, 72 (3%) of patients experienced a SCD event during the following up period (0.8%/year). There was no association between any comorbidities and the risk of SCD. While this is a large cohort study, the major limitation that one must consider is that past medical history was assessed at the initial clinical evaluation. It, therefore, does not reflect the development of new comorbidities over the follow-up period (which may have a different impact on arrhythmia risk). Additionally, a major comorbidity, obstructive sleep apnea, was not examined, which has important pathogenesis links to arrhythmias. Lastly, the number of patients with adjudicated SCD was low and may be underpowered to detect associations between comorbidities and ventricular arrhythmias.

The authors should be congratulated for completing this important study which demonstrates that in this cohort of HCM patients, comorbidities did not play a significant role in risk of arrhythmias (atrial or ventricular). This adds and confirms previous publications that failed to establish a strong association between obesity and adverse arrhythmic outcomes^{3,8}. The data presented in this paper is important and surprising. The lack of association with arrhythmic risk given the plethora of data on patient comorbidities in non-HCM cohorts, and especially considering that obesity in HCM can lead to a more severe phenotype and worse disease progression⁹ is not entirely understood and requires further exploration.

One potential explanation is the application of body mass index (BMI) to define obesity. Although BMI is largely ingrained as the most conventional and convenient method to define obesity, it can be an imprecise measurement as it defines overall adiposity and doesn't consider the different elements of adiposity distribution such as abdominal vs. epicardial adipose tissue (EAT). EAT is an evolving area of interest given its proximity to cardiac tissue, and its presence and size have been associated with cardiac arrhythmias, particularly atrial fibrillation¹⁰. EAT is proposed to play a role in arrhythmogenesis by altering the electrical and structural properties of the cardiac myocardium¹¹. Specifically, direct infiltration and promotion of fibrosis can set up the correct environment for reentry. Further, paracrine effects by adipokines can lead to ion channel modulation and alteration of cell-cell electrical coupling. Our knowledge of the role of EAT in HCM is limited. Muhib et al.¹² in a cohort of 62 patients, showed an increased incidence of AF related to an increase in EAT, even when adjusted for baseline characteristics. Further examination of this in larger cohorts may be insightful.

Overall, the authors provide a thought-provoking paper that adds critical data to the HCM literature. As we broaden our understanding of the elements and measurement of obesity and other comorbidities, perhaps it will become an important risk stratification tool. Until then, the role of comorbidities and its impact on AF or SCD in this subset of patients with HCM remains unclear and further research is warranted.

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