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EDITORIAL

The Importance of Sex Differences in Patients with Hypertrophic Cardiomyopathy – Tailoring Management and Future Perspectives

Sex-related differences in epidemiology, phenotype and outcome have been documented in several cardiovascular conditions, ranging from coronary artery disease to valvular heart disease and, ultimately, heart failure with preserved ejection fraction (HFpEF) and hypertrophic cardiomyopathy (HCM).[1] To date, however, these differences have not been fully incorporated into practice guidelines, nor translated into tailored diagnostic and management strategies.

In the last decade, sex differences in patients with HCM have sparked interest both at clinical and laboratory levels. In this issue, Huang and colleagues present the clinical characteristics and outcome of 576 patients diagnosed with HCM from 2008 to 2016 at West China Hospital of Sichuan University.[2] In their report, after a mean follow up of 3.2 ± 2.3 years, the rate of rehospitalization related to heart failure was significantly higher in female patients ($n = 260$, 46% of the entire cohort) compared to men. However, there were no gender-related differences in HCM–related mortality and age–adjusted all–cause mortality, even though women were diagnosed and referred for specialty care later than men, had higher left ventricular outflow tract (LVOT) gradients, more severe symptoms at baseline and atrial fibrillation, and more commonly developed advanced heart failure at follow–up.

OLDER AND MORE SYMPTOMATIC WOMEN

For the last 50 years, HCM has shown a male predominance, with men reaching up to 55–60% of most published cohorts,[3–5] including the present study – a trend which is seen consistently and irrespective of the geographical region of origin. A male predominance should come as unexpected, given the autosomal dominant inheritance pattern of HCM and the expected 50/50, male/female ratio. This discrepancy may be partially explained by both differences in biological and pathophysiological markers of cardiovascular disease and exposure to different social behaviors (related to symptom recognition, interpretation or decision-making) and stressors.[1] Taken together, these elements may lead to bias in diagnosis and ultimately late recognition of HCM in women. Late diagnosis in women has been well characterized in other cardiovascular conditions relatable to atypical symptoms and different response to environmental conditions. As a case in point, women with chest pain were shown to wait longer before calling emergency units, resulting in pre-hospital delays in accessing treatment.[6] Whether this may apply to genetic cardiomyopathies such as HCM, is still unclear. The results presented by Huang in part confirm this trend as women were older than men, on average by 4 years at the time of HCM diagnosis.

Similar to other US and European reports, in this study, women reported dyspnea more often (46.5% vs 38.3% in men, $P = 0.046$) with a higher prevalence of patients in NYHA III/IV (46.9% vs 30.7% in men, $P < 0.001$) at baseline. Notably, use of loop diuretics was almost twice as high in women. Accordingly, women were significantly more likely to require HCM-related hospitalization.

GENDER AT THE HEART OF THE PROBLEM

Recently, it was found that exercise performance is diffusely impaired in women with HCM compared with men, particularly after mid-life, a phenomenon largely unrelated to obstruction. Furthermore, exercise performance, which was previously shown to predict outcome in HCM as a whole, appeared to have a true predictive value in male patients only, while the occurrence of clinical endpoints in females was largely independent of exercise capacity.[7]

Occurrence of exercise-induced obstruction was lower in women, suggesting that, while a substantial proportion of HCM men may owe their reduced performance to provocable LVOT gradients, this is often not the case in women. Rather, these findings point to more severe degrees of myocardial dysfunction in female patients, which become overt after mid-life. That exercise impairment may be related to intrinsic myocardial dysfunction (associated with high degrees of microvascular dysfunction and myocardial fibrosis), rather than dynamic obstruction, appears relevant to the adverse prognosis of HCM women, as their form of heart failure seems to be less “reversible” and tends to progress despite optimal medical care.

As confirmed by Huang and colleagues, female HCM patients tend to have smaller left ventricular cavity size, associated with lower stroke volumes and higher diastolic filling pressures during effort (thus explaining the high prevalence of NYHA III/IV and dyspnea). It is tempting to speculate that tailored activities and well-conducted training programs might provide a safe and effective measure to overcome functional impairment associated with gender in post-menopausal women.[8]

Finally, disparities have been noted also in terms of invasive management of obstructive HCM (HOCM). Despite significant differences at clinical presentation, in a large series of 2506 patients referred for septal myectomy, after adjustment for critical baseline prognostic

factors, there was no survival difference after septal myectomy by gender. One may thus speculate that optimal care of women with HOCM should focus on earlier identification of disease and prompt surgical referral of appropriate patients who do not respond to medical treatment.[9]

FUTURE PERSPECTIVES

New pharmacological approaches might soon provide therapeutic opportunities for patients with HOCM. Mutations in β-cardiac myosin alter force generation and promote hypercontractility in HCM. In particular, mutations responsible for HCM seem to affect the stability of myosin molecules in the super-relaxed state, which is characterized by slow ATP hydrolysis rate, leading to a change in the number of myosin heads accessible to actin. This super-relaxed state corresponds to a folded-back conformation of myosin heads observed in muscle fibers around the thick filament backbone. While human β-myosin exists in these two states, mutations in HCM disrupt this balance, leading to excessive energetic costs.[10] A new drug which works as allosteric reversible myosin inhibitor (Mavacamten – MYK-461) was designed to reversibly inhibit β-myosin binding to actin and promote the super-relaxed conformation.[10]

Encouraging preliminary data showed that the molecule suppresses ventricular hypertrophy, cardiomyocyte disarray, myocardial fibrosis, and attenuated hypercontractility in animal HCM models,[11] and increased exercise tolerance, thereby improving symptoms in humans.[12] A phase 3 double-blind clinical study to evaluate Mavacamten in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy (EXPLORER- HCM – NCT: NCT03470545) has terminated enrollment of 220 patients with HOCM and results are awaited in 2020. The primary endpoint in the study is a combination of change in NYHA functional class and in peak VO2 determined by CPET from baseline to treatment week 30.

Another cardiac myosin inhibitor developed for symptomatic HOCM (CK-274) is currently undergoing a phase 1 trial (NCT: 03767855). Safety and tolerability data are soon expected.

In this scenario, these drugs offer promising and intriguing therapies for women who, being obstructive and symptomatic more frequently, may benefit most from early disease diagnosis and prompt therapy initiation.

DECLARATION OF COMPETING INTEREST

The author has no financial or other conflicts of interest to disclose.

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