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Adding clinical value with coronary flow assessment in hypertrophic obstructive cardiomyopathy

Hypertrophic obstructive cardiomyopathy (HCM) is an inherited myocardial disease commonly caused by mutations of genes encoding proteins of the cardiac sarcomere, Z-disc, and calcium-controlling proteins that, in the typical setting, leads to septal hypertrophy (wall thickness $\geq$ 15 mm) not related to abnormal loading conditions, and associated with left ventricular obstruction (LVOT) greater than or equal to 30 mm Hg [1]. HCM may manifest clinically with exercise-induced shortness of breath and/or angina pectoris, palpitations, atrial fibrillation, and syncope [1,2]. Despite longevity of the majority of HCM patients, a certain percentage of these patients is at risk to develop predominantly diastolic but also systolic heart failure as well as sudden cardiac death owing to ventricular arrhythmia. The clinical suspicion of HCM is commonly confirmed by echocardiography and/or cardiac magnetic resonance imaging (CMR) by determining the septal wall thickening and LVOT [1]. Delayed-enhancement (DE) on CMR images to signify interstitial fibrotic alterations and/or changes in myocardial angiotensin II type 1 receptors [3,4], however, may signify a more advanced stage of HCM with important diagnostic and prognostic implications [1]. Apart from medical and interventional treatment options to address symptomatic patients, the cardiovascular risk stratification is a matter of ongoing debate [1,5–7]. The guidelines to stratify the cardiovascular risks in HCM patients include an array of parameters such as age, a family history of sudden cardiac death, unexplained syncope, left atrial size, left ventricular wall thickness, LVOT, abnormal blood pressure response, and non-sustained ventricular tachycardia [2,8]. In the individual HCM patient, these guidelines, however, may be seen as suboptimal given their low positive and modestly high negative predictive values for cardiac prognostication [1,8]. In this respect, stress-rest myocardial perfusion and flow assessment with positron emission tomography (PET) has provided new insights into the function of the coronary circulation and distribution of coronary flow [9–11]. For example, Yalcin et al. [9] demonstrated that diffuse subendocardial hypoperfusion and regional myocardial ischemia in the area of left-ventricular wall thickening owing to microvascular dysfunction contributes to the development of transient LV cavity dilation in symptomatic HCM. Notably, hyperemic myocardial blood flow (MBF) increases were substantially lower in those with transient LV cavity dilation than in those without (1.6 ± 0.7 vs 2.3 ± 1.0 ml/min/g). In line with previous observations [7,12], the assessment of the transmural MBF gradient, an indicator of subendocardial perfusion, unraveled markedly lower MBF values in those with than in those without transient LV cavity dilation (0.85 ± 0.22 vs 1.09 ± 0.39 ml/g/min). It is also important to keep in mind that the transient LV cavity dilation is not only related to diffuse subendocardial hypoperfusion but also in part owing to enhanced LVOT during vasomotor stress related to vasodilator-induced increase in heart rate and afterload reduction accompanied by an increase in LVOT obstruction leading to elevated left ventricular end-diastolic pressure [9]. The increase in left ventricular end-diastolic pressure likely compresses the subendocardial layer and, thereby, further aggravates subendocardial hypoperfusion during vasomotor stress. Interestingly, Magnusson et al. [7] reported the transmural MBF gradient (applying ^{15}O-water and PET) in conjunction with suboptimal myocardial oxygen consumption and myocardial external efficiency (determined with ^{11}C-acetate and PET) to be predictive for NSVTs, appropriate ICD shocks and secondary ICD indications in HCM. These observations in conjunction with seminal outcome PET flow studies in HCM [12,13], are also confirmed by a recent ^{13}N-ammonia and PET flow study [14]. In the latter study, sustained ventricular arrhythmia outcome was stratified by the hyperemic MBF heterogeneity index (MBF-HI = highest regional MBF/lowest regional MBF) in symptomatic HCM patients. As it was observed [14], a hyperemic MBF-HI $\geq$ 1.85 had a significantly higher risk for the manifestation of sustained ventricular arrhythmias than those with a hyperemic MBF-HI < 1.85 in these symptomatic HCM individuals. In particular, the MBF-HI proved to be an independent predictor of both sustained and non-sustained VT thereby adding incremental prognostication to clinical and structural heart assessment [14].

In this issue of the IJC Heart & Vasculature, de Oliveira Antunes et al. [15] provide a unique and comprehensive state-of-the-art article addressing the variety of cardiac phenotype expression of hypertrophic cardiomyopathy, range of clinical symptoms, cardiovascular risk stratification, medical and interventional treatment in symptomatic HCM patients. In particular, there is an increasing awareness that microvascular dysfunction in HCM patients without obstructive CAD may indeed account not only for symptoms such as exercise-related chest pain and shortness of breath but also for worsened clinical outcome [7,12–14]. Pronounced microvascular dysfunction can indeed cause global subendocardial hypoperfusion during vasomotor stress that may result in a dysbalance between oxygen supply and myocardial demand leading to myocardial stunning. These periods of coronary microvascular dys-

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function induced myocardial stunning during times of increased metabolic demand is likely to account patient not only for chest pain symptoms but also for shortness of breaths and fatigue in HCM [9,15]. Indeed, adding PET determined coronary flows to routine echocardiographic/CMR evaluation of the heart morphology is anticipated to further optimize the identification of HCM patients with microvascular dysfunction who are likely to benefit from novel pharmacotherapies symptomatically and improved prognostication leading to appropriate ICD implantation that deserves further investigations in large-scale and well-designed clinical trials.

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Research data related to this submission

No data were used for the research described article in the article.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100512.

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