IJC Heart & Vasculature 26 (2020) 100467

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.journals.elsevier.com/ijc-heart-and-vasculature

Emergence of endocardium/epicardium flow gradient as novel risk biomarker in patients with hypertrophic cardiomyopathy

Patients with hypertrophic obstructive or non-obstructive cardiomyopathy (HCM) may not only present with angina pectoris or syncope but they may also be at risk for sudden cardiac death (SCD) owing to ventricular arrhythmia [1]. As many HCM patients have an excellent longevity, cardiac risk stratification for the identification of those individual who are likely to benefit from an implantable cardioverter-defibrillator (ICD) is needed. The risk stratification guidelines commonly implies parameters such as a family history of SCD, unexplained syncope, left ventricular wall thickness, abnormal blood pressure response, and non-sustained ventricular tachycardia (NSVT) [2], while age, left atrial size, and left ventricular outflow obstruction have been added more recently [3]. Whereas these guidelines have been firmly established, they may be seen as suboptimal as they have low positive and modestly high negative predictive values for cardiac risk prediction [3,4]. Myocardial ischemia and/or microvascular dysfunction, in particular in the area of left ventricular wall thickening, may not only lead to angina symptoms but also to replacement fibrosis and SCD in HCM patients [5,6]. As regional ischemia can cause a shortening of action potential, dispersion of left ventricular repolarization, and induction of re-entrant arrhythmias potentially leading to SCD, it is somehow surprising that the cardiac risk stratification in the primary prevention does not include the assessment of myocardial perfusion and flow in HCM. More recently, it has also been realized that late-gadolinium enhancement on cardiac magnetic resonance imaging, as a non-invasive probe for interstitial fibrosis, may also reflect another important parameter for a further refine the cardiac risk stratification in HCM [1]. In this issue of the IJC Heart & Vasculature, Magnusson et al. [7] provide unique information of some association between a stress-related endocardium/epicardium flow gradient and the prevalence of NSVT in HCM that may suggest such flow gradient as potential novel risk biomarker. As it was observed, in a total of 25 HCM patients, 40% (n = 10) had NSVT defined as 3 consecutive beats of ventricular origin $\geq$ 160 bpm reported on ICD stored electrogram within a 12 months follow-up period. The composite endpoint of sustained ventricular arrhythmias exceeding 30 s with hemodynamic compromise, cardiac arrest, and appropriate ICD therapy with either antitachycardia pacing or discharge was noted in 32% (n = 8) patients. In this small HCM population, the mean myocardial blood flow (MBF) at rest (adjusted for hemodynamics) was 0.91 ml/g/min, while the pharmacologically-stimulated hyperemic flow was markedly decreased with a mean value of 1.59 ml/g/min. Using ^{15}O-water and PET, the threshold to identify normal hyperemic MBFs is commonly exceeding 2.3 ml/g/min [8]. Despite the structural abnormality of the myocardium in HCM patients, normal hyperemic MBFs and myocardial flow reserve (MFR = MBF hyperemia / MBF rest) have been reported with both positron-flow tracers ^{15}O-water and ^{13}N-ammonia and PET, respectively [6,9,10]. Thus, the septal wall thickening and structural alterations of the myocardium per se may not cause microvascular dysfunction and, thus, reductions in hyperemic flow increases. What kind of functional and structural alterations in the arterial wall in conjunction with an increase in left ventricular wall thickness lead to microvascular dysfunction still remains to be elucidated. In the current study [7], the authors evaluated also a transmural MBF gradient (endocardium/epicardium quotient) which was normal at rest with a mean value of 1.14 ml/g/min but abnormally decreased to 0.92 ml/g/min during pharmacologic stress. Of note, the MBF gradient during pharmacologic stress was significantly lower in HCM patients with NSVT (p = 0.022) and borderline for rest MBF (p = 0.059) but not for global stress and rest MBFs. Such observations emphasize the transmural decrease in stress-stimulated flow as a more sensitive MBF parameter in the identification of functional and/or structural alterations of the coronary arterial wall than global MBFs [11–13]. It would have been of interest to evaluate these flow parameters also for regional flows and flow gradient in the area of the thickened and non-thickened left ventricular myocardium to provide more detailed insights but these regional flow parameters unfortunately were not reported. Further interesting information is derived from measuring the myocardial oxygen consumption (MVO2) with ^{11}C-acetate and PET that unraveled higher values in the NSVT group, while 0.088 ml/g/min in the whole study group. Using ^{11}C-meta-hydroxyephedrine (^{11}C-HED) with PET to assess myocardial sympathetic innervation, the mean retention index was 0.11 min^{-1}, a higher volume of distribution or transmural gradient of clearance rate, or lower clearance rate demonstrated a non-significant trend of association with NSVT. It is likely that the current study population was not large enough or, conversely, that the range of ^{11}C-HED related parameters was not wide enough to reach statistical significance with the prevalence of recorded NSVTs. The study conducted by Magnusson et al. [7] adds further important and unique information that an abnormal decrease in transmural MBF during pharmacologic stress is associated with NSVT and, in part, also with a composite endpoint of appropriate ICD therapy and secondary ICD indication in HCM patients. If such observations [7] are confirmed in a larger HCM population, then the assessment of hyperemic MBFs or

https://doi.org/10.1016/j.ijcha.2019.100467

transmural flow gradient with cardiac PET may indeed reflect a unique tool to contribute to a further refinement of the primary risk stratification in HCM patients. Albeit that an implantable ICD system effectively terminates life-threatening arrhythmias, long-term risk of complications, such as device infection or inappropriate shock therapy, necessitate an optimal patients selection [14]. Advanced imaging to assess function and morphology of the left ventricle with cardiac PET and magnetic resonance imaging [7,15] is expected to further optimize the identification of those HCM patients who are likely to benefit most from the implantation of an ICD but needing further confirmation in clinical investigations.

Sources of funding

This work is supported by a departmental fund from Washington University (No. 12-3271-93128).

Disclosure

Dr. Schindler has received research support from NIH (1RO1HL142297-01A1) and from GE Healthcare.

Research data related to this submission

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

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2019.100467.

References

[1] B.J. Maron, S.R. Ommen, C. Semsarian, P. Spirito, I. Olivotto, M.S. Maron, Hypertrophic cardiomyopathy: present and future, with translation into contemporary cardiovascular medicine, J. Am. Coll. Cardiol. 64 (2014) 83–99.
[2] S. Poli, D. Facchin, F. Rizzetto, et al, Prognostic role of non-sustained ventricular tachycardia detected with remote interrogation in a pacemaker population, Int. J. Cardiol. Heart. Vasc. 22 (2019) 92–95.
[3] C. O'Mahony, F. Jichi, M. Pavlou, et al, A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD), Eur. Heart J. 35 (2014) 2010–2020.
[4] B.J. Gersh, N.J. Maron, R.O. Bonow, et al, ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American college of cardiology foundation/american heart association task force on practice guidelines, Circulation 124 (2011) (2011) 2761–2796.
[5] P.E. Bravo, S.L. Zimmermann, H.C. Luo, et al, Relationship of delayed enhancement by magnetic resonance to myocardial perfusion by positron emission tomography in hypertrophic cardiomyopathy, Circ. Cardiovasc. Imaging 6 (2013) 210–217.
[6] H. Yalcin, I. Valenta, F. Yalcin, et al, Effect of diffuse subendocardial hypoperfusion on left ventricular cavity size by (13)N-ammonia perfusion PET in patients with hypertrophic cardiomyopathy, Am. J. Cardiol. 118 (2016) 1908–1915.
[7] P. Magnusson, J.H. Nordstrom, H.J.M. Lubberink, F. Gadler, J. Sorensen, S. Moerner, Positron emission tomography (15O-water, 11C-acetate, 11C-HED) risk markers and nonsustained ventricular tachycardia in hypertrophic cardiomyopathy, Int. J. Cardiol. Heart. Vasc. 26 (2020) 100452, https://doi.org/10.1016/j.ijcha.2019.100452.
[8] I. Danad, V. Uusitalo, T. Kero, et al, Quantitative assessment of myocardial perfusion in the detection of significant coronary artery disease: cutoff values and diagnostic accuracy of quantitative [(15)O] H2O PET imaging, J. Am. Coll. Cardiol. 64 (2014) 1464–1475.
[9] T.H. Schindler, V. Dilsizian, Coronary microvascular dysfunction: clinical considerations and noninvasive diagnosis, JACC. Cardiovasc. Imaging 11 (2019), https://doi.org/10.1016/j.jcmg.2018.11.036.
[10] F. Cecchi, I. Olivotto, R. Gistri, R. Lorenzoni, G. Chiriatti, P.G. Camici, Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy, N. Engl. J. Med. 349 (2003) 1027–1035.
[11] I. Valenta, A. Antoniou, W. Marashdeh, et al, PET-measured longitudinal flow gradient correlates with invasive fractional flow reserve in CAD patients, Eur. Heart. J. Cardiovasc. Imaging. 18 (2017) 538–548.
[12] I. Valenta, A. Quercioli, T.H. Schindler, Diagnostic value of PET-measured longitudinal flow gradient for the identification of coronary artery disease, JACC, Cardiovasc. Imaging 7 (2014) 387–396.
[13] I. Danad, P.G. Raijmakers, H.J. Harms, et al, Impact of anatomical and functional severity of coronary atherosclerotic plaques on the transmural perfusion gradient: a [15O]H2O PET study, Eur. Heart J. 37 (2016) 2068–2080.
[14] M. Ogano, Y.K. Iwasaki, I. Tsuboi, et al, Mid-term feasibility and safety of downgrade procedure from defibrillator to pacemaker with cardiac resynchronization therapy, Int. J. Cardiol. Heart. Vasc. 22 (2019) 78–81.
[15] S. Leng, X. Zhao, A.S. Koh, et al, Age-related changes in four-dimensional CMR-derived atrioventricular junction velocities and displacements: Implications for the identification of altered annular dynamics for ventricular function assessment, Int. J. Cardiol. Heart. Vasc. 22 (2019) 6–12.

Thomas H. Schindler *
Mallinckrodt Institute of Radiology, Division of Nuclear Medicine, Washington University School of Medicine, St. Louis, MO, USA

Cardiovascular Division, John T. Milliken Department of Internal Medicine, Washington University School of Medicine, St. Louis, MO, USA
* Corresponding author at: Washington University in St. Louis, Mallinckrodt Institute of Radiology-Division of Nuclear Medicine, 510 S. Kingshighway, Campus Box 8223, St. Louis, MO 63110, USA.
E-mail address: thschindler@wustl.edu

Ines Valenta
Mallinckrodt Institute of Radiology, Division of Nuclear Medicine, Washington University School of Medicine, St. Louis, MO, USA

Sudhir Jain
Cardiovascular Division, John T. Milliken Department of Internal Medicine, Washington University School of Medicine, St. Louis, MO, USA

Received 28 December 2019
Accepted 30 December 2019

Available online 6 January 2020