Transient ischemic dilation in hypertrophic cardiomyopathy: A complex sign in a complex disease

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Left ventricular (LV) cavity dilation, better known as transient ischemic dilation (TID), is an indirect marker of ischemia in myocardial perfusion imaging, already described in Thallium-201 scans several years ago. The proposed mechanisms for this abnormality are related to the presence of severe stress-induced ischemia.¹ A first possible explanation is the occurrence of more pronounced ischemia in the subendocardial layer of the myocardium, with consequent apparent enlargement of the ventricular cavity.² Alternatively, the systolic dysfunction due to ischemia could persist until the moment of image acquisition, according to the model of myocardial stunning, and the ensuing reduction in wall motion and thickening cause an apparent decrease in myocardial uptake due to the partial volume effect, which is mainly recognizable as an enlarged ventricular cavity.³ Experimental evidences have confirmed that a true increase in LV end diastolic dimensions is relatively rare, whilst a larger end systolic volume, with the additional consequence of a decrease in LV ejection fraction (EF) is a commonplace observation.³ Independently of the true mechanism, and most probably because they are often both involved, TID has been found to be a very important and reliable sign of severe ischemia.^{1,4} This has been confirmed within all different modalities of myocardial perfusion imaging,

including all used tracers, stressors, and protocols, although various definitions and cutoff values have been proposed. Its sensitivity for the detection of multivessel coronary disease ranged from 38% to 80%, and its specificity was consistently higher than 90%.^{1,4} However, in the general population of patients studied for suspect or known epicardial coronary artery disease its incidence is quite low, probably less than 10%.⁵

TID IN HCM

Beside diffuse and severe epicardial coronary artery disease, microvascular dysfunction (MVD) is another possible cause of diffuse ischemia and thus the substrate of TID. In patients with hypertrophic cardiomyopathy (HCM), the importance given to ischemia, mainly caused by MVD, has constantly grown in the last years.⁶ However, early observations of abnormalities in myocardial perfusion imaging already demonstrated quite a high proportion of subjects with TDI in HCM, although initially the focus on the ruling out of epicardial coronary artery disease limited the interest for this particular finding. In 1987, O’Gara et al. described not only the various patterns of regional perfusion defects in Thallium-201 SPECT, registering them in 41 of 72 HCM patients but also mentioned the occurrence of TDI in 26 cases (thus 36%).⁷ Few years later, Sugihara et al. observed TID in 24 of 50 patients; moreover, the comparison with volume measurement performed using radionuclide ventriculography let the authors conclude that in these patients TID was related to subendocardial ischemia, and not to true end-diastolic dilation of the left ventricle.⁸ Cannon et al. found TDI in 26 of 50 patients, and in 11 of them it was the sole abnormality. In these latter patients, there were high end-diastolic ventricular pressures demonstrating ischemia-related abnormalities in LV filling.⁹ In the following years, other authors, who focused their attention to the presence of TID as a sign

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of subendocardial ischemia, reported percentages ranging from 35% to 45%.¹⁰ Therefore, all these studies converge in indicating that TID is far more prevalent among patients with HCM than with coronary artery disease, and point to subendocardial ischemia caused by MVD as the predominantly involved mechanism.

TID AND QUANTITATIVE PET

Given these premises and the circumstance that PET is the best approach to identify and classify MVD in HCM, it is not surprising that, as soon as gated PET has entered in practice, TID has been observed and reported. The first study by Bravo et al. was focused on the relationship among myocardial blood flow (MBF), functional parameters, and LV outflow tract obstruction (OTO) in HCM patients submitted to dipyridamole stress.¹¹ As regards to TID, they observed a value > 1.13 in 8 of 21 patients (38%) without persistent LVOTO (differentiated between subjects without LVOTO and those in whom it was registered just under provocation). Conversely, the rate was 10/12 (83%) in the 12 patients with fixed LVOTO. The Authors did not find any relation between LVOTO and the changes in MBF and myocardial flow reserve (MFR) caused by dipyridamole, but did not explicitly address the issue of a possible relationship between TID occurrence and MBF changes. With regard to this, their sole statement was that TID and LVEF drop were common findings in HCM patients.¹¹ The same group focused on the relationship between TID and MBF in a later study on a larger cohort.¹² They divided the population according to the presence of TID > 1.13 , which was observed in 32 of 61 patients. The patients with TID had more severe perfusion abnormalities, lower peak MBF and worse LVEF response to stress than the other patients. Moreover, only the presence of stress-induced perfusion defects and peak MBF were found to be significant predictor of TID. Another interesting observation of the study was that the degree of TID decreased with time (from 2–4 minutes to 15 minutes after vasodilator stress) in the patients with abnormal TID, but not in those without.¹² Finally, Yalçin et al. expanded the comparative analysis on patients with vs without TID in an even larger population of more than hundred cases, showing that the TID-positive patients had lower stress LVEF, larger stress perfusion defects and lower peak MBF and MFR than the patients without TID.¹³ Moreover, the authors tried to separate the assessment of MBF in the subendocardial and subepicardial layers of the LV wall, registering a significantly lower peak subendocardial MBF in the TID-positive patients than in the other subjects, while the subepicardial peak MBF was not significantly different between the two groups.

Consequently, the subendocardial/subepicardial MBF ratio was significantly different under stress between the two groups.¹³ This last observation is in good agreement with the studies performed on HCM patients with the purpose of evaluating the behavior of subendocardium in hypertrophic ventricles. Various reports describe the presence of a more impaired peak subendocardial MBF in HCM patients as compared to controls or patients with other forms of LV hypertrophy.^{14,15} Moreover, one of these studies identified the reduced peak subendocardial MBF as a possible cause of stress-induced LVEF drop in HCM patients, with demonstration of increased end-systolic volumes after stress in these subjects.¹⁶

VASODILATOR PET VS EXERCISE ECHOCARDIOGRAPHY

In this scenario that consistently correlates TID with stress-induced MBF abnormalities and possibly ischemia in HCM patients, the results of the study by Lu et al. published in this issue of the Journal of Nuclear Cardiology are somehow dissonant.¹⁷ In a large patient population, whose overlap with those of previous studies by the same group is unclear, they did not find any relation between the presence of significant TID in perfusion PET and the results of exercise echocardiography. In particular, the patient group with TID > 1.13 in dipyridamole PET showed no differences in the echocardiographic volumes after peak exercise from the patients without PET TID, and just one patient of the whole cohort showed post exercise TID in echocardiography. Furthermore, there was no relationship between the electrocardiographic signs of ischemia observed during vasodilator PET and those registered during exercise echocardiography. On the other hand, there was a significantly lower global longitudinal strain in the patents with PET TDI, thus showing a greater impairment of mechanics, independently of the similarly preserved LVEF in the two groups. Finally, the authors did not register differences in the outcome of the patient groups during the follow-up.

How can these results be reconciled with the above-mentioned wide consensus on TID importance and significance in patients with HCM? Apparently, their behavior under exercise is almost invariably normal as far as systolic LV function is investigated, independently of the occurrence of TID in vasodilator PET. However, the authors themselves express a word of caution about the volumetric comparisons, since the PET assessment coincides with stress while the echocardiographic examination has been performed after peak exercise (with a time interval that is not declared). As mentioned above, in the setting of vasodilator PET the decrease in TID from early to more delayed images is

known. Thus, it could be hypothesized that delayed imaging would miss a short-duration TID. It could be as well worth mentioning that despite a quite good reported reproducibility, the observer-related uncertainties of echocardiographic measurements are larger than 10 mL and thus not completely negligible in front of end-systolic volumes that average 20 mL.

POSSIBLE INSIGHTS IN HCM PATHOPHYSIOLOGY

However, reducing the explanation of the disagreement between PET and exercise echocardiography for TID occurrence to pure technical issues would deprive the study of most of its value and, more importantly, would miss the potential meaning of these differences as an indicator of the complex disease pathophysiology. First of all, the finding of lower global longitudinal strain confirms that the patients with PET TID are affected by a more severe involvement, albeit it does not reach the level of systolic dysfunction. Second, the detection of electrocardiographic signs suggests that ischemia can be induced by exercise in these patients even if without necessarily affecting the wall motion pattern in a recognizable way. Previous data comparing exercise Thallium-201 SPECT and exercise echocardiography had demonstrated that perfusion defects could be present without corresponding changes in echocardiographic volumes, but with signs of effort-related diastolic dysfunction.¹⁸ It must be also considered that according to the protocol exercise echocardiography was performed for the general assessment of HCM, and not specifically for the suspicion of inducible ischemia. Thus, it can be supposed that most attention was devoted to the assessment of dynamic LVOTO and not to fine echocardiographic signs of inducible ischemia.

Another, and probably more intriguing point, to consider for explaining the disagreement between vasodilator PET and exercise echocardiography is the relative role of subendocardial ischemia vs LV stunning (and thus LV end-systolic dilation) as possible causes of TID itself. Although for various above-mentioned reasons an underestimation of transient LV dysfunction in post-exercise echocardiography cannot be completely ruled out, there are no doubts that echocardiography is unable to visualize the LV wall perfusion if ultrasonographic contrast media are not employed. Therefore, it cannot be excluded that in the PET images, together with a more pronounced transient LV dysfunction, subendocardial ischemia was the prevalent cause of TID. Unfortunately, and differently from a previous report by the same group, in the present study the separate analysis of the two main LV wall layers was not performed, so it is impossible to get a positive

confirmation of this hypothesis. Certainly, in spite of its pathophysiological attractiveness, the detection of true subendocardial ischemia using PET is a complex task, and the potential interference of heart motion because of breathing and ventricular contraction remains to be effectively eliminated. Most recently, the intrinsic impossibility of a reliable estimate of layer MBF has been suggested, according to logical reasoning, mainly focused on the interaction between heart rate and apparent MBF distribution.¹⁹ However, this negative deduction does not fit with the reported experimental data, which indicated the detection of decreased subendocardial MBF just in a proportion of patients within groups showing the very same heart rate response to vasodilator stress.

A last argument is the possibility that, in case of MVD as the main mechanism of ischemia (and thus of TID), the different pathophysiology of exercise vs vasodilator stress could be reflected by a different capability to elicit the conditions that cause TID. In other words, in HCM the prominent role of MVD for producing ischemia, and the different mechanism through which exercise and vasodilators influence MBF and MFR, could lead to a disparity in the occurrence of TID that was not observed so far in patients examined for coronary artery disease. As the authors correctly point out, the impossibility to obtain a reliable measurement of MBF during exercise precludes a definitive demonstration of this last explanation. It must be also considered that supine exercise (the sole that could be attempted for quantitative PET) is not equivalent to the standard upright exercise, and therefore, could not give comparable results. Most recently, the greater capability of upright treadmill exercise vs semi-supine cycling for eliciting LVOTO in HCM has been reported and this observation supports the complex relationship between HCM and exercise.²⁰

CONCLUSION

In conclusion, the study by Lu et al. does not fit perfectly in the previously outlined scenario of high TID prevalence in HCM because of MVD-related (subendocardial) ischemia. Beyond possible methodological explanations that could have affected the comparison between vasodilator PET and exercise echocardiography, however, the result disagreement could suggest a quite intriguing relationship among type of stimulation, ability to elicit MVD abnormalities, and capacity of the latter to reach the level needed to cause true ischemia. Although it appears quite counterintuitive that the stimulation that directly affects myocardial oxygen consumption seems less effective in producing ischemia than maximal vasodilation of the resistance vessels, we

cannot exclude that this could be the result of the peculiar blood flow impairment caused by MVD and of the interaction on it of other factors, such as for instance the sympathetic drive related to exercise. Therefore, the study by Lu et al. does not give the expected answers, but possibly help us conceiving new questions about the role of a complex sign such as TID in a complex disease such as HCM.

Disclosure

Roberto Sciagrà has nothing to disclose.

References

- McLaughlin MG, Danias PG. Transient ischemic dilation: A powerful diagnostic and prognostic finding of stress myocardial perfusion imaging. *J Nucl Cardiol* 2002;9:663-7.
- Iskandrian AS, Heo J, Nguyen T, Lyons E, Paugh E. Left ventricular dilatation and pulmonary thallium uptake after single-photon emission computer tomography using thallium-201 during adenosine-induced coronary hyperemia. *Am J Cardiol* 1990;66:807-11.
- Van Tosh A, Hecht S, Berger M, Roberti R, Luna E, Horowitz SF. Exercise echocardiographic correlates of transient dilatation of the left ventricular cavity on exercise thallium-201 SPECT imaging. *Chest* 1994;106:1725-9.
- Weiss AT, Berman DS, Lew AS, Nielsen J, Potkin B, Swan HJ, et al. Transient ischemic dilation of the left ventricle on stress thallium-201 scintigraphy: A marker of severe and extensive coronary artery disease. *J Am Coll Cardiol* 1987;9:752-9.
- Hansen CL, Sangrigoli R, Nkadi E, Kramer M. Comparison of pulmonary uptake with transient cavity dilation after exercise thallium-201 perfusion imaging. *J Am Coll Cardiol* 1999;33:1323-7.
- Maron MS, Olivetto I, Maron BJ, Prasad SK, Cecchi F, Udelson JE, et al. The case for myocardial ischemia in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2009;54:866-75.
- O'Gara PT, Bonow RO, Maron BJ, Damske BA, Van Lingen A, Bacharach SL, et al. Myocardial perfusion abnormalities in patients with hypertrophic cardiomyopathy: Assessment with thallium-201 emission computed tomography. *Circulation* 1987;76:1214-23.
- Sugihara H, Shiga K, Umamoto I, Harada Y, Katahira T, Nakagawa T, Nakamura T, Matsubara K, Terashima S, Azuma A, Katsume H, Nakagawa M. Assessment of transient dilation of the LV cavity in patients with hypertrophic cardiomyopathy by exercise thallium-201 scintigraphy. *Kaku Igaku* 1990;27:1281-9 [in Japanese].
- Cannon RO 3rd, Dilsizian V, O'Gara PT, Udelson JE, Schenke WH, Quyyumi A, et al. Myocardial metabolic, hemodynamic, and electrocardiographic significance of reversible thallium-201 abnormalities in hypertrophic cardiomyopathy. *Circulation* 1991;83:1660-7.
- Kawasaki T, Sugihara H. Subendocardial ischemia in hypertrophic cardiomyopathy. *J Cardiol* 2014;63:89-94.
- Bravo PE, Pinheiro A, Higuchi T, Rischpler C, Merrill J, Santaularia-Tomas M, et al. PET/CT assessment of symptomatic individuals with obstructive and nonobstructive hypertrophic cardiomyopathy. *J Nucl Med* 2012;53:407-14.
- Bravo PE, Tahari A, Pozios I, Luo HC, Bengel FM, Wahl RL, et al. Apparent left ventricular cavity dilatation during PET/CT in hypertrophic cardiomyopathy: Clinical predictors and potential mechanisms. *J Nucl Cardiol* 2016;23:1304-14.
- Yalçin H, Valenta I, Yalçin F, Corona-Villalobos C, Vasquez N, Ra J, et al. Effect of diffuse subendocardial hypoperfusion on left ventricular cavity size by ¹³N-Ammonia perfusion PET in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 2016;118:1908-15.
- Knaapen P, Germans T, Camici PG, Rimoldi OE, ten Cate FJ, ten Berg JM, et al. Determinants of coronary microvascular dysfunction in symptomatic hypertrophic cardiomyopathy. *Am J Physiol Heart Circ Physiol* 2008;294:H986-93.
- Sciagrà R, Passeri A, Cipollini F, Castagnoli H, Olivetto I, Burger C, et al. Validation of pixel-wise parametric mapping of myocardial blood flow with ¹³NH₃ PET in patients with hypertrophic cardiomyopathy. *Eur J Nucl Med Mol Imaging* 2015;42:1581-8.
- Sciagrà R, Calabretta R, Cipollini F, Passeri A, Castello A, Cecchi F, et al. Myocardial blood flow and left ventricular functional reserve in hypertrophic cardiomyopathy: A ¹³NH₃ gated PET study. *Eur J Nucl Med Mol Imaging* 2017;44:866-75.
- Lu DY, Yalçin H, Sivalokanathan S, Greenland GV, Vasquez N, Yalçin F, et al. Higher incidence of vasodilator-induced left ventricular cavity dilation by PET when compared to treadmill exercise-ECHO in hypertrophic cardiomyopathy. *J Nucl Cardiol* 2018. <https://doi.org/10.1007/s12350-018-01521-x>.
- Isobe S, Izawa H, Takeichi Y, Nonokawa M, Nanasato M, Ando A, et al. Relationship between exercise-induced myocardial ischemia and reduced left ventricular distensibility in patients with nonobstructive hypertrophic cardiomyopathy. *J Nucl Med* 2003;44:1717-24.
- Sambucetti G, Morbelli S, Bellini A, Marini C. Radionuclide imaging of subendocardial ischaemia: An insight into coronary pathophysiology or a technical artefact? *Eur J Nucl Med Mol Imaging* 2017;44:861-5.
- Reant P, Dufour M, Peyrou J, Reynaud A, Rooryck C, Dijos M, et al. Upright treadmill vs semi-supine bicycle exercise echocardiography to provoke obstruction in symptomatic hypertrophic cardiomyopathy: A pilot study. *Eur Heart J Cardiovasc Imaging* 2018;19:31-8.