Why LV dilatation with vasodilator stress in hypertrophic cardiomyopathy?

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Transient ischemic dilatation (TID) of the left ventricle (LV) on vasodilator stress perfusion images is a concerning sign. In some, TID may reflect global subendocardial hypoperfusion during stress.[1] A reduction in subendocardial perfusion results in an increase in observed chamber size on the stress images and the finding of TID. However, in patients with advanced coronary disease (CAD), TID during vasodilator stress might also reflect transient LV dysfunction due to generation of an actual myocardial oxygen supply/demand imbalance (true ischemia). TID on vasodilator stress PET perfusion images has previously been correlated with impaired myocardial perfusion reserve and with an acute decline in LV systolic function during stress.[2] Moreover, patients with TID on vasodilator PET images exhibit poorer clinical outcomes as compared to those without TID who have similar LV ejection fractions and perfusion defect scores.[3] Thus, TID on vasodilator stress images in CAD patients may reflect global subendocardial hypoperfusion, induction of a true oxygen supply/demand imbalance with ischemic LV dysfunction, or both.

LV DILATATION IN HCM

Acute LV dilatation on vasodilator stress images has also been observed in hypertrophic cardiomyopathy (HCM) patients, being reported in 55% of HCM patients without significant CAD.[4] However, the mechanism of LV dilatation in HCM patients has not been examined as fully as that in CAD patients. In this issue of the Journal, Bravo and co-authors correlate the findings on regadenoson stress $^{13}NH_3$ perfusion studies and amyl nitrite augmented echocardiography to provide a more in-depth look at the potential mechanisms for TID in HCM patients.[5] In a retrospective analysis of 61 symptomatic HCM registry patients, they identified 32 individuals who exhibited TID during vasodilator stress PET perfusion imaging and 29 who did not. Both groups of patients were of similar age and gender composition and had similar medication use. The prevalence of diabetes, dyslipidemia, atrial fibrillation, hypertension, chest pain, dyspnea, syncope, sudden death, family history of HCM, and sudden death was also comparable in both groups.

At the time of the PET perfusion studies, rest and stress heart rates, rest LV ejection fractions and rest and stress blood pressures were similar in both patient groups. Stress LV ejection fractions were significantly lower in the patients with TID than in those without TID (40 ± 9% vs 53 ± 9%, $P < .0001$) and patients with TID exhibited greater declines in EF during stress (−17 ± 9% vs −3 ± 7%). HCM patients with TID had greater maximal LV wall thicknesses on echocardiography than those without TID (2.2 ± 0.5 vs 1.8 ± 0.3 cm, $P < .001$) and in a statistical model including both continuous and categorical variables, the authors found that the only clear correlates of LV chamber dilatation were abnormal rest and hyperemic myocardial perfusion values and the degree of left ventricular hypertrophy.

EARLY VS LATE TID RATIOS

One unique feature of the present study is that reformatted dynamic PET images were used to measure ratios of ventricular volumes at early (2-4 min) and late (15-20 min) time points following regadenoson administration. This allowed the authors to determine if there was a temporal change in TID ratios in their subjects. The early ratios correspond to times typically reported with vasodilator PET imaging.[2,3] The late TID

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measurements more closely correspond to times at which TID is assessed on vasodilator SPECT perfusion images.[6] It should be noted that the cut-off value used to define an abnormal TID index in the present report (1.13) was based upon studies employing rubidium-82 and not $^{13}NH_3$ as the perfusion tracer. Rubidium-82 emits a positron that is more energetic than $^{13}NH_3$, meaning that the tissue travel distances prior to positron annihilation are greater than that with the later tracer. Thus, it is not clear that 1.13 value used by the authors to define TID was indeed the optimal value for the $^{13}NH_3$ images. Moreover, the authors have not determined if there are differences in TID indices for the early and late $^{13}NH_3$ image sets in normal subjects.

Because of the increases in heart rate generally observed with vasodilator stress, heart rates at the time of acquisition of the early images would be expected to be higher than those at the time of late image acquisition. Summed early non-gated images would be expected to have a larger systolic component (as a percent contribution to the image set) than the later images and would therefore be anticipated to be of smaller volume. If so, this should result in smaller early TID ratios than late TID ratios. In fact, this is not what the authors found. In patients with left ventricular dilatation, early TID ratios were significantly higher than late TID ratios (1.30 ± 0.13 vs 1.27 ± 0.12, $P = .001$) whereas there was essentially no difference in early and late TID ratios in subjects without transient ventricular dilatation (1.04 ± 0.08 vs 1.04 ± 0.07, $P = .9$). Thus, the factor or factors provoking ventricular dilatation in the HCM patients must have had a greater influence on ventricular volumes per se than the influence of stress-related changes in heart rate.

RELATIONSHIP TO AMYL NITRITE ECHOCARDIOGRAPHY

On echocardiography, mean LV ejection fractions, end-systolic, and end-diastolic volumes were similar in both groups. Mean LV outflow tract gradients at rest and during amyl nitrite provocation tended to be higher in those with TID than in those without TID, but the differences were not statistically significant. Twelve of the 32 (38%) patients with TID had outflow tract obstruction at rest ($n = 6$) or with amyl nitrite provocation ($n = 6$). Only one (3%) of 29 patients without TID had outflow tract obstruction at rest, while 13 (45%) had inducible obstruction with amyl nitrite provocation. Overall, the proportion of patients with LV outflow tract obstruction (at rest or during amyl nitrite provocation) was higher (48%) in those without LV TID than in those with TID (38%) during vasodilator stress. This suggests that LV outflow tract obstruction per se is unlikely to be directly related to TID on vasodilator stress images in HCM patients.

MACROVASCULAR VS MICROVASCULAR ISCHEMIA

Only thirty-five (57%) of the patients had invasive angiography to exclude obstructive CAD, and this is a study limitation. The authors note that most subjects without angiography were less than 50 years of age and thus unlikely to have obstructive CAD. For the present study, coronary lesions were considered obstructive if the luminal stenosis on visual analysis was >50%. However, if a diseased coronary vessel supplies very thicken myocardium it is possible that a coronary lesion of less than 50% could have a physiologic consequence. Thus, it is not possible to entirely exclude a confounding influence of macrovascular disease on the authors' findings.

Visually identified reversible perfusion defects (summed difference scores of 2 or greater) were identified in 97% of those with TID, and in 41% of those without TID $P < 0.0001$); summed difference scores were significantly greater in those with TID than those without TID (7.6 ± 6.3 vs 2.3 ± 2.8, $P < .0001$). Maximal global hyperemic blood flows and perfusion reserves were smaller in the patients with TID (1.56 ± 0.40 vs 2.18 ± 0.39 ml/min/g, $P < .0001$ and 1.95 ± 0.49 vs 2.57 ± 0.68, $P < 0.0001$) than in those without TID. In all patients, peak myocardial perfusion and perfusion reserves were lower in the septum and the inferior walls than in the lateral and anterior walls, with TID positive patients exhibiting more pronounced regional reductions in peak perfusion and perfusion reserves than those without TID. In association with the more profound reductions in LV systolic function noted during stress, the authors' findings are consistent with the induction of ischemic left ventricular dysfunction as a major cause of TID in the HCM patients.

The authors' findings are consistent with prior invasive studies in HCM patients demonstrating regionally decreased lactate consumption during rapid atrial pacing,[7] with prior noninvasive PET studies demonstrating regional abnormalities in perfusion, perfusion reserves, and metabolism in HCM patients[4,8-10] and with the demonstration of vasodilator-induced abnormalities in subendocardial perfusion identified on cardiac MRI.[11,12] In the absence of epicardial coronary disease, factors contributing to the induction of tissue ischemia in HCM patients include thickening of intramural coronary arterioles, increases in regional wall stress resulting from increases in intra-cavity pressures in individuals with outflow obstruction, disorganized cellular architecture with an increase in collagen in the

interstitium, and ventricular hypertrophy with a decrease in capillary density.[13]

PERFUSION PATTERNS ASSOCIATED WITH LV DILATATION

The authors reported three different patterns of myocardial perfusion with stress in HCM patients exhibiting TID. In 14 patients (44%) the stress images demonstrated prominent perfusion defects in trabeculations and papillary muscles that were clearly visible within the LV cavity on the rest perfusion images (Type 1 pattern). Individuals exhibiting the Type I pattern tended to have slightly greater LV wall thicknesses and the majority (79%) had global perfusion reserves greater than 2.00. While the perfusion defects may have resulted in apparent ventricular dilatation, it is also possible that ischemia of the papillary muscles/trabeculae might have had an impact on actual ventricular volumes. As subendocardial structures, the papillary muscles are sensitive to ischemia in hypertrophied ventricles, and localization of inducible perfusion defects to prominent trabeculations/papillary muscles is consistent with the notion that focal subendocardial ischemia was visualized on the PET studies. It would be of interest to know if transient ischemic mitral insufficiency might have influenced the stress ventricular volumes observed in these patients.

In the second perfusion pattern associated with TID ($n = 12$ patients, 38%), localized stress perfusion defects were identified in the most hypertrophied myocardial segments. Patients exhibiting the type II pattern had the largest reversible perfusion defects (greatest summed difference scores) and the smallest myocardial perfusion reserves (only 17% had global flow reserves greater than 2.00). Presumably, larger segmental myocardial thicknesses resulted in greater compromise of perfusion during stress. A striking reversible defect is shown in the septum in Figure 4 of the paper. One wonders if vasodilator stress might have also have resulted in acute RV dilatation in this patient, due to potential compromise of perfusion in the RV septum.

Six of the HCM patients with LV dilatation (18%) exhibited no apparent reason for the acute LV dilatation (Type III pattern). Although reversible defects were identified in these subjects, the summed difference scores were smaller than in those with the Type I and Type II patterns and the decreases in LV ejection fractions during stress tended to be smaller than those in the other groups as well. This type of pattern may perhaps reflect a global decrease in subendocardial flow with vasodilator stress, resulting in apparent LV dilation.

STUDY IMPLICATIONS

The study by Bravo and colleagues provides additional evidence that myocardial ischemia is associated with TID during vasodilator stress in patients with HCM. Ischemia likely results from impaired perfusion at the microvascular level with possible additional compromise due ''non-obstructive lesions'' in diseased coronary vessels supplying thickened myocardium. The findings suggest that HCM patients may exhibit a variable degree of regional impairment of perfusion with stress. Some HCM patients with mildly decreased hyperemic tissue perfusion and perfusion reserves demonstrate little or no deterioration in function and do not exhibit ventricular dilation with vasodilator stress. Individuals with a more prominent impairment in perfusion may exhibit diffuse subendocardial hypoperfusion and reductions in LV systolic function during vasodilator stress. In some, localized perfusion defects in papillary muscles and/or the most hypertrophied ventricular segments may be visualized and tend to be associated with greater decreases in LV systolic function. As exemplified in the Type 1 and Type II case illustrations in this paper, induction of localized ischemia also offers the potential for secondary impairment of papillary muscle and/or right ventricular function. Further clinical studies appear necessary to test this hypothesis. Finally, prospective studies are needed to determine if clinical patient outcomes differ according to the type of stress pattern identified in HCM patients on myocardial perfusion imaging. If localized perfusion defects in hypertrophied segments or papillary muscles do reflect more profound degrees of regional ischemia, then HCM patients displaying these scintigraphic patterns of perfusion might be expected to have poorer clinical outcomes than those displaying the Type III pattern. As such, this investigation by Bravo and colleagues provides insights into the LV dilatation observed with vasodilator stress in some HCM patients and suggests additional hypotheses which can be tested by well-designed clinical studies.

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