Do we really need to look at volumetric measurements with ^{99m}Tc single photon emission computed tomography (SPECT) myocardial perfusion imaging?

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A little less than a century ago, in their classical work, Tennant and Wiggers[1] observed in open-chest dogs that within 60 seconds of coronary occlusion myocardial contractions in the ischemic zone change from active shortening to passive systolic lengthening. After restoration of myocardial blood flow, contractile dysfunction was reversed. In later animal work, Heyndrickx and colleagues[2] demonstrated that while regional electrocardiograms normalize within seconds, contractile dysfunction lasts for up to 2 hours after a 5-minute occlusion and for up to 24 hours after a 15-minute occlusion. The functional effects in the ischemic myocardium were shown to persist longer than one could have been predicted by the rapid normalization of coronary flow. The concept of myocardial stunning was born—and defined as a state of prolonged contractile dysfunction of post-ischemic myocardium in which myocardial function is gradually restored over time.

Post-ischemic stunning can be quantified on single photon emission computed tomography (SPECT)—myocardial perfusion imaging (MPI) from regional wall motion abnormalities or more globally as a reduction in left ventricular ejection fraction (LVEF). Another marker for myocardial stunning is the increase in LV volumes after stress, namely transient ischemic dilatation (TID) that is considered indicative of severe and extensive coronary artery disease and a poor prognostic sign.[3,4] These parameters have been investigated by a staggering number of studies and their added diagnostic and prognostic value is undisputed.[5–8] Reliable assessment and quantification of myocardial stunning by SPECT-MPI pose however a series of challenges on the applied imaging protocols. First, the timing of the image acquisition is key. The time elapsed between stress testing and image acquisition determines the severity of post-stress LVEF decrease.[9] Further, if the delay between stress and rest image acquisition is too short to allow for recovery of myocardial contractility, the post-stress EF decrease may be underestimated.[10] Second, the type of stress agent may influence the severity of stress. Although the initial investigations on TID were performed by physical stress,[4] more recent studies have confirmed these results by vasodilator stress.[7] Last but not least, measurement of LVEF and LV volumes might be limited by SPECT-MPI given its spatial resolution. The pathophysiological mechanism of these phenomena is also a highly debated subject. Some authors see it as true increase in LV volume due to post-ischemic stunning and offer several potential mechanisms for the increased contractility (i.e., enhanced venous return via Frank-Starling, increased myocardial blood flow via Gregg mechanism and/or by higher heart rate).[11,12] Others explain it by a stress-induced subendocardial hypoperfusion giving the visual impression of dilatation on ungated SPECT.[13,14] Nonetheless, the severity of post-ischemic stunning differs between the different stress agents: it seems that myocardial dysfunction persists much longer after dobutamine than after

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adenosine stress.[12,15,16] All these challenges may affect the accurate and reliable estimation of myocardial stunning and could result not only in high inter- and intra-patient variability but also between different SPECT scanners and image acquisition protocols.

In the current issue of the *Journal of Nuclear Cardiology*, Camm et al.[17] address some of these challenges in a large retrospective study. The variation in TID and LVEF decrease from rest to stress was analyzed in a—rather normal—population including 661 gated and 992 ungated patient studies without inducible perfusion defects. Mean LVEF in gated SPECT images decreased slightly but significantly from rest (62.4%) to post-stress images (61.2%) resulting in a mean LVEF difference of 1.2% (standard deviation of 5.2%). The mean TID ratio was 1.00 with an overall upper 95% confidence limit of 1.23. With lower volumes on ungated rest images, the upper 95% confidence limit rose to 1.37. The authors, therefore, concluded that a fall in LVEF of more than 11.6% (= 1.2% + 2 × 5.2%) and TID ratio of more than 1.23 is required for clinically relevant myocardial stunning.

The authors should be commended for elaborating on the normal limits of variation in LV volumes and EF in a large patient population. However, the generalizability of their results is limited due to the single-center design (with a two-headed SPECT camera and one-day stress-rest ^{99m}Tc-tetrofosmin acquisition protocol) and due to the fact that about 30% of the initial patient population was excluded from the analysis. Another factor that confines the application of their results is the fact that patients were stressed by exercise (56%) or by regadenoson (42%). From a pathophysiological view, it would have been of great interest whether these groups differed with regard to LVEF decrease and TID ratio. Without this subgroup analysis, the different stressors rather appear to be a limitation than an advantage of this study. The authors' results highlight the enormous variability of these parameters in apparently normal SPECT-MPI studies. A strength of the study is the aim to focus on patients without inducible perfusion defects. Nonetheless, the authors included patients with fixed perfusion defects and with balanced ischemia in their analysis, something that could potentially explain the large variability of their data. Besides this debatable diagnostic reference standard, the study lacks information on the outcome of these patients.

It is unclear whether it is safe to defer a patient with an LVEF decrease from rest to stress of 9% and a TID of 1.15. Previous outcome studies have demonstrated that a decrease in LVEF of more than 10% in patients without inducible perfusion defects increases the risk for future cardiac events.[8,18] Hence, the threshold of 11.6% in the present study reflects previous results relatively well and adds valuable real-world data on volumetric measurements like LVEF decrease in gated or TID in ungated SPECT images.

Gauging the clinical implications of these results, the low sensitivity of TID deserves particular mention. In view of the dramatic decrease in prevalence of pathological SPECT-MPI scans,[19] the issue of the clinical value of markers for myocardial stunning like TID should come into discussion. With non-invasive assessment of coronary artery disease shifting towards lower-risk patients, our tools need to have appropriate sensitivity to be useful in clinical routine. In this new era of non-invasive cardiovascular imaging, one could suggest that such highly specific markers might gradually lose significance—until the day that a SPECT-MPI study pops up without inducible perfusion defect but a fall in LVEF of 15% and a TID of 1.3. This patient with severe three-vessel disease and balanced ischemia will be grateful that you looked at the volumetric measurements of his test.

Disclosures

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