Should early post-stress imaging be performed on a routine clinical basis for myocardial perfusion studies?

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Establishing imaging protocols for radionuclide myocardial perfusion imaging (as with any other radiotracers used in nuclear medicine) always requires some sort of trade-off in order to obtain an “optimal” imaging protocol.¹ Various considerations must be taken into account before finalizing recommendations for imaging with a specific agent. Even after general consensus in the medical literature, new clinical data or new type of equipment or softwares could and should modify the “standard” imaging protocol guidelines.² Among those parameters, considerations must be applied to the “practicality” of the imaging protocol in a day-to-day clinical setting in order to answer the clinical question in a reasonable time-frame. Before obtaining the optimal protocol for a myocardial perfusion imaging agent, data on several parameters must be known such as, but not limited to, dosimetry (physical, biological, and effective half-lives), biological characteristics (biodistribution and pharmacokinetics, degree of myocardial uptake and retention, the presence or not of myocardial redistribution, level of activity in the adjacent organs to the heart, and the relationship between myocardial uptake and coronary blood flow). In addition, the impact of a given imaging protocol on the overall diagnostic accuracy (sensitivity, specificity, the ability to detect

the true extent and degree of perfusion defects, and appropriate results using either pharmacologic or exercise stress testing) must be evaluated.

When 99mTc-sestamibi (Cardiolite) was introduced into clinical research in the late 1980s (and later on 99mTc-tetrofosmin, Myoview), researchers noted that the pulmonary activity was negligible even immediately after its injection, the blood clearance had a half-life of 4 minutes at rest and 1.6 minutes at stress, the biological half-life for the liver was approximately 30 minutes after a rest or exercise injection.³ The myocardial uptake is approximately 1.5% of the injected 99mTc-sestamibi dose, while the liver and biliary uptake represents almost 30% of the injected dose. The effective half-life of clearance (which includes both the biological half-life and the physical half-life of 99mTc, or radionuclide decay) for the heart was approximately 3–4 hours, and for the liver was approximately 30 minutes after a rest or exercise injection. Therefore, the ideal imaging time should reflect the best compromise between high myocardial count rate and the lowest surrounding organ uptake (mostly liver and gallbladder).

Considering the potential variability of hepatic clearance through the biliary tree (variable hepatobiliary transit time), and possible related “subdiaphragmatic contamination,” and considering that there is no clinically relevant myocardial redistribution within few hours after its administration, it was initially recommended to wait approximately 60–75 minutes after 99mTc-sestamibi intravenous injection before starting the image acquisition.^{4,5} Subsequently, different approaches have been proposed in order to decrease this relatively long-time interval between injection and imaging.⁶ Although initially the liver uptake was seen as a potential cause of image artifacts, it was soon recognized that the hepatobiliary excretion would more likely affect the imaging protocols (bowel activity). Some “recipes” such as the

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oral administration of water, cream, or fatty meal has been used to increase the biliary excretion. However, this increased rate of excretion of biliary activity may cause a “collateral damage” such as a rapid increased uptake into the duodenum (and then the rest of the bowel), which may be positioned adjacent to the heart (or may sometimes reflux into the stomach, which lies immediately adjacent to the inferior wall of the left ventricle (LV), secondary to an entero-gastric reflux, causing a more persistent and more prominent uptake).⁷ According to the location, extent and intensity of this subdiaphragmatic tracer concentration, significant imaging artifacts can be created, causing either an inferolateral wall myocardial perfusion defect (“negative ramp filter” artifact) or a focal artifactual increased inferior wall count density (Compton scattering activity). According to the type of image artifact (false increase or decrease uptake) and its time of occurrence (on the rest or the stress study), this may have a significant clinical impact on the overall diagnostic accuracy of the test. Since this hepatobiliary clearance pattern is variable and hard to predict in a given patient, a unique imaging protocol is likely to be more difficult to apply.

Therefore, since the clinical introduction of 99mTc-labeled myocardial perfusion imaging agents in the early 1990s, various imaging protocols, including the rest and stress injection sequence and the time interval between intravenous injection and the beginning of image acquisition, have been described in the literature.⁸ Published ASNC (American Society of Nuclear Cardiology) imaging guidelines specify the optimal minimum delays for both 99mTc-sestamibi and 99mTc-tetrofosmin. For 99mTc-sestamibi, the recommended minimum delays between radiotracer administration and imaging are 15-20 minutes for exercise, 45-60 minutes for rest, and 60 minutes for pharmacologic stress and for 99mTc-tetrofosmin the minimum delays are 10-15 minutes for exercise, 30-45 minutes for rest, and 45 minutes for pharmacological stress. The differences between the two radiotracers are related to the difference in their respective biological characteristics. It is noteworthy that although these guidelines are well established, and that more recently published data clearly show the feasibility and the advantages of early imaging, many clinical sites in various countries are still using the imaging parameters initially described when these agents have been introduced, that is a delay of 60-75 minutes or more.

In this current issue of the *Journal*, Mut et al⁹ report the results of a prospective multicenter study performed in 229 patients from seven countries on the detection of post-exercise stunning using early gated SPECT myocardial perfusion imaging. They evaluated the feasibility and the value of early post-stress imaging

(15 ± 5 minutes) compared to the traditional delayed imaging (60 ± 15 minutes) with 99mTc-sestamibi. There was no statistically significant difference in the quality of the images from both sets of post-stress studies. The images were judged of excellent quality in 93% of the early images and in 95% of the delayed images. Furthermore, there were no studies considered uninterpretable due to increased subdiaphragmatic radiotracer accumulation. Most patients (97%) had exactly the same summed difference score and in the 63 patients with ischemia, the assignment to the ischemic group was similar for both early and delayed images. These data were obtained specifically after exercise. These results confirm those previously reported.^{10,14}

The other endpoint of their study was to use early gated SPECT imaging to detect post-exercise myocardial stunning in patients with coronary artery disease (CAD) defined as a transient post-ischemic LV dysfunction induced by a brief episode of severe ischemia in the absence of irreversible cellular damage and after the restoration of baseline coronary blood flow. Post-ischemic stunning was first observed almost 40 years ago in animal models of coronary artery occlusion and reperfusion.^{15,16} The severity and duration of regional LV dysfunction depend on the severity of the ischemic insult as well as the metabolic condition of the myocardium before the insult. Information on time course of the resolution of ischemia-induced LV dysfunction after completion of exercise in patients is limited and inconsistent. However, although some studies have shown that regional dyssynergy may persist up to few hours after completion of exercise, it is generally accepted that LV dysfunction tends to resolve more rapidly, usually within 30 minutes.^{17,18} Large studies demonstrated that post-stress LV ejection fraction (EF) and end-systolic volume obtained by gated SPECT using 99mTc-labeled myocardial perfusion imaging agents provided significant information over the extent and severity of perfusion defects in prediction of future cardiac events.^{19,20} Therefore, evaluation of LV EF at rest and post-stress and LV volumes may detect transient ischemic LV dysfunction and provides important prognostic information.

Several studies showed that one of the main advantages of 99mTc-labeled myocardial perfusion imaging is the ability to perform simultaneous noninvasive assessment of both LV function and myocardial perfusion. The regional myocardial uptake of the radiotracer represents the relative myocardial perfusion pattern at the time of the tracer injection, but the gated SPECT represents LV function at the time of image acquisition, which can be from 15 to 60 minutes or even more after injection. Therefore, gated SPECT imaging performed earlier after radiotracer administration could

potentially detect more post-exercise LV dysfunction.²¹ Mut et al⁹ showed that the change in the LV EF in patients with ischemia was greater between the rest and the early stress imaging than between the rest and delayed stress studies. Unfortunately, as pointed out by the authors, wall motion or thickening was not assessed nor clinical data on the prognostic value from change in LV ejection fraction was obtained. Clinical data with rubidium-82 myocardial positron emission tomography performed very early after vasodilation stress demonstrated that LVEF reserve provided significant independent and incremental value to Rubidium-82 myocardial perfusion imaging for predicting the risk of future adverse events.²²

Technical factors and perfusion patterns must be taken into consideration before using LV EF changes as a measurement of the presence of myocardial stunning. A gated SPECT acquisition of 16 frames per cardiac cycle instead of 8 frames per cycle (as frequently reported) should be used to better represent the heart motion during a single cardiac cycle to minimize temporal under sampling bias and provide a more accurate assessment of LV EF.²³ A study performed with a dynamic mathematic cardiac torso phantom examined the impact of perfusion pattern and imaging sequence on the accuracy of gated SPECT perfusion in determining LV volumes and ejection fraction.²⁴ They found that both myocardial perfusion and imaging sequence had a significant influence on LV function assessment. Post-stress end-diastolic and end-systolic volumes increased, and EF decreased in simulated phantoms with large stress perfusion defects. Both large perfusion defects and the use of a stress-rest same day injection sequence resulted in an EF decrease as measured by quantitative gated SPECT. Consequently, a myocardial “stunning artifact” was frequently observed when using the stress-rest sequence. In view of these considerations, the usual gated SPECT definition of myocardial stunning (which is defined as a 5% decrease in EF between stress and rest studies) might be reconsidered, using more clinical data with early post-stress imaging performed in a wide variety of patients with proven CAD.^{21,25,26} The criteria of a change of 5% also seems to be too “sensitive” for stunning definition, given the intrinsic variability of LV EF assessment with gated SPECT, especially using only 8 frames per cycle, thus significantly limiting the temporal resolution of the study.

In summary, early post-exercise myocardial gated SPECT study may provide additional information on potential post-ischemic stunning as well as transient dilatation of the left ventricle or increased lung uptake, which are all markers indicative of severe CAD and can be used as prognostic factors. More importantly, this is done without altering the overall quality of the images.

One of the advantages of early post-stress imaging after intravenous administration is that data acquisition can always be repeated later, should the subdiaphragmatic activity be judged to be too significant on early imaging. Furthermore, the decrease time interval between radiotracer injection and image acquisition may positively affect the patient’s scheduling and throughput, especially in a laboratory with a heavy workload. Medical literature already reported sufficient data to conclude that “early” SPECT myocardial perfusion imaging may provide good quality diagnostic studies so that it may be used as a “standard” procedure. However, more data will be needed before imaging guidelines can be modified in order to validate some data acquisition parameters and criteria of interpretation. Well-controlled prospective studies performed in patients with proven CAD and in whom the presence of myocardial stunning will be corroborated with one or more other imaging modalities will allow for a more robust definition of stunning using gated SPECT imaging. The proposed “minimum” delays for imaging in different guidelines might become “standard” delays in future guidelines. Having a better definition and validation of the gated SPECT criteria for myocardial stunning is mandatory before suggesting its wide clinical application. Nevertheless, early post-stress imaging seems to be a very promising alternative to the so-called “standard” myocardial perfusion imaging protocol with 99mTc-labeled radiotracers.

Disclosure

Raymond Taillefer has no conflicts of interest or financial ties to disclose.

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