EDITORIAL

Combined assessment of myocardial perfusion and left ventricular function by nuclear cardiology: The value of high-efficiency SPECT

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The introduction of ECG gating to myocardial perfusion SPECT imaging (MPI) more than 20 years ago provided the opportunity for the combined assessment of myocardial perfusion and left ventricular (LV) function with a single radiotracer injection.[1] Software for automatic quantification of left ventricular volume and ejection fraction (EF) was developed, and ECG-gated SPECT became a widespread, routine part of MPI acquisition and interpretation.[2] Although simultaneously acquired, myocardial perfusion images represent coronary flow distribution at peak stress, whereas gated images demonstrate LV function at the time of acquisition. It has soon been realized that stress-induced ischemia was frequently associated with lower post-stress EF than resting EF.[3] This post-stress stunning phenomenon of global LV function was further supported by the identification of post-stress regional wall motion abnormality, indicating severe obstructive coronary artery disease (CAD).[4]

Post-stress stunning is transient in nature, and recovers often over 60 minutes after stress cessation.[5] Its early detection using a conventional Anger-camera is limited by several technologically inherent pitfalls: First, the need to wait for at least 15 minutes, and sometimes up to 60 minutes following a radiotracer injection before initiating image acquisition because of hepatic uptake;[6,7] second, acquisition time itself is very long, frequently more than ten minutes, allowing partial recovery of the LV function during the acquisition itself. Thus, acquiring images at peak stress or very early post-stress using a conventional camera is unfeasible. Nevertheless, previous studies demonstrated the added diagnostic value of conventional post-stress gated SPECT in the detection of severe coronary artery disease, and the incremental prognostic value of post-stress EF and end-systolic volume over the extent, and severity of perfusion defects in predicting future cardiac events.[8]

In this issue of the *journal,* Brodov et al from Cedars-Sinai Medical Center and Oregon Heart and Vascular Institute demonstrated for the first time the feasibility to obtain early gated stress acquisitions of acceptable quality using a high-efficiency SPECT camera, and to detect early stunning and its recovery over time. They evaluated 50 patients who underwent regadenoson same-day rest/stress MPI, using the D-SPECT CZT camera (Spectrum Dynamics, Caesarea, Israel). Following regadenoson and Tc-99m injection, sequential 2-minute acquisitions were performed starting at 1, 5, 9, 13, and 17 minutes, and a last 4-minute acquisition starting 21 minutes following injection. The first acquisition, starting one minute after injection was of unacceptable quality, and discarded from the analysis. EF reserve was calculated as the absolute difference between stress and rest EF for each of the sequential post-stress acquisitions. Significant ischemia was defined as ischemic total perfusion deficit $\geq$5%, and a 50-patient group was divided into two subgroups based on this cutoff value. The results demonstrated that patients with ischemia had negative EF reserve with the most negative mean value of $-$4.2% depicted at the

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earliest acquisition (5th minute), followed by a gradual recovery throughout the subsequent acquisitions, reaching −1.5% at the 21st minute acquisition. In contrast, patients without significant ischemia had a positive EF reserve at all post-stress acquisitions. The difference between the ischemic and non-ischemic subgroups was significant at the two earliest acquisitions (5th and 9th minute). The EF response after regadenoson compared to resting EF is shown at Figure 1. Baseline resting EF was lower among ischemic vs non-ischemic patients. Among ischemic patients, stress EF dropped at the 5th minute compared to rest, and partially recovered at the 9th minute acquisition. Among non-ischemic patients, EF increased from the initial stress acquisition. Considering the very short time to peak effect of regadenoson on coronary flow of 20-40 seconds, and the short duration of sustained increased flow velocity after 0.4 mg regadenoson of greater than 2.5 times the baseline being 2.3 minutes,[9] the observed negative EF reserve at the current study of −4.2%, measured during the 5th to 7th minutes after injection probably missed the timing of maximal hyperemia, and underestimated the maximal negative EF response among the ischemic patients. Nevertheless, the feasibility of early, fast imaging using a CZT camera has been demonstrated, capturing negative EF reserve among ischemic patients, and positive EF reserve among non-ischemic patients.

The results of this study are concordant with previous studies assessing the EF reserve, using regadenoson Rb^{82} PET-MPI.[10,11] Hsiao et al. demonstrated that patients with normal PET-MPI had higher EF reserve compared to patients with mild reversible defects, and to those with moderate to severe defects (6.5%, 4.3% and −0.2%, respectively, $P < .05$).[10] Patients with high angiographic score of jeopardized myocardium had the lowest EF reserve, whereas those

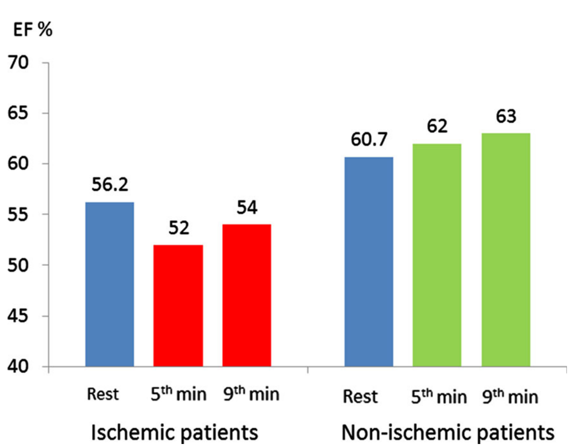

Figure 1. Rest and early post-stress EF at 5th and 9th minute acquisitions, among patients with ischemia compared to patients without ischemia. EF indicates ejection fraction.

with low likelihood of CAD had the highest EF reserve (−2.8% vs 7.2%, $P < .0001$). Dorbala et al. demonstrated that annualized rate of all-cause mortality and cardiac events was significantly higher among patients with EF reserve <0% compared to those with EF reserve ≥0%.[11] LVEF reserve provided independent and incremental value to Rb-82 MPI for predicting risk of death and cardiac events. It seems that CZT-MPI is capable of identifying patients with ischemia and EF reserve <0%, similar to PET-MPI. EF reserve by CZT-MPI has not yet been related to the severity of angiographic CAD, and its prognostic value has not been assessed. However, the good image quality obtained by early, fast CZT imaging, and the magnitude of post-stress EF drop in the current study, which was larger than EF decrease reported in PET-MPI studies is promising, and warrant further evaluation and assessment of clinical applicability. Intuitively, a negative early EF reserve would potentially be an important ancillary finding among patients with reversible perfusion defects, supporting the diagnosis of significant CAD, and suggesting more extensive disease with larger extent of jeopardized myocardium compared to positive EF reserve. It would be challenging to demonstrate a diagnostic benefit in the context of extensive CAD and balanced hypoperfusion associated with only mild ischemia or even normal MPI. In this setting, the assessment of early EF reserve could potentially increase the sensitivity of MPI.

Based on the current study, a single, early 2-minute acquisition starting 5 minutes after injection or even earlier has the potential to capture the lowest possible value of the EF reserve and detect post-stress stunning following regadenoson administration. It is important to obtain this acquisition at a time window after blood washout of the radiotracer and before significant liver uptake appears, without missing pick effect of regadenoson (2 to 5 minute after tracer injection). It should be noted that this early, short acquisition provides data on ventricular function, and an additional, full time acquisition should be obtained later, after 20 to 60 minutes, for assessment of myocardial perfusion. This study used regadenoson as the pharmacological vasodilator; however, extrapolation to other vasodilators is probably feasible, similar to Rb^{82} PET-MPI protocols.[11]

An important issue to address is the relatively high dose of Tc-99m sestamibi administered in the current study. A stress dose of 32-42 mCi Tc99m sestamibi translates to effective radiation of 9-12 mSv. Adding rest and stress doses results in a total per-study dose of 40-53 mCi, representing a total effective dose of 12-16 mSv. These radiation doses are far higher than ASNC goal of radiation reduction, namely <9 mSv in at least 50% of the nuclear studies performed.[12] Using a highly efficient CZT camera is a major tool for dose reduction

Table 1. Advantages of CZT-SPECT imaging

Advantage	Clinical benefit
High spatial resolution	High image quality Improved diagnostic accuracy
Short acquisition time	High patient throughput Less motion artifacts Prone imaging
Low-dose protocols	Reduced radiation exposure
Stress-first protocol	High percentage of stress-only studies
High-energy resolution	Simultaneous dual-isotope imaging: Tc-99m sestamibi/I-123 MIBG
Dynamic imaging	Myocardial blood flow and Myocardial perfusion reserve
Early stress acquisition	EF reserve

in cardiac SPECT. Previous studies demonstrated the feasibility and diagnostic accuracy of half-dose protocols, using either rest-stress or stress-first imaging sequence, at the expense of slight prolongation of imaging time.[13-16] The feasibility of a low-dose early post-stress imaging is questionable, even using a CZT camera. Obviously, acquisition time would need to be longer than two minutes, and a half-dose protocol will dictate doubling imaging time to 4 minutes. Yet, a 4-minute acquisition, starting within 5 minutes after tracer injection will potentially capture a negative EF reserve.

CZT-SPECT technology has been shown to provide important advantages over conventional Anger cameras which upgraded the field of nuclear cardiology (Table 1). The high sensitivity of CZT detectors to gamma photons, the efficient, direct conversion of photons into electrical signal, and focusing on the heart provide fast imaging with high myocardial count-rate, and high spatial resolution.[17] These imaging characteristics result in high image quality and improved diagnostic accuracy. Therefore, CZT-MPI has been referred to as ''PET-like'' imaging modality. In addition, the short acquisition time allows high patient throughput, lower rate of motion artifacts, and the ability to perform routine, prone imaging in every patient to improve specificity, even in very busy nuclear laboratories.[15] Low-dose protocols have been validated, leading to a significant reduction in patient radiation exposure, and the ability to meet the ASNC recommendation.[12] The high image quality of low-dose images facilitated the use of stress-first protocols, involving a low stress dose, with the optional conversion to stress-only after a normal stress.[15,18] Using the Discovery 530 NM (GE Healthcare, Haifa, Israel), our group has recently demonstrated that high image quality, stress-only MPI can be accomplished with effective radiation doses as low as 1.5 mSv.[15] The high-energy resolution characteristic of the CZT detectors allows simultaneous acquisition of dual-isotope protocols, such as Tc-99m-sestamibi/I-123 MIGB studies for assessment of myocardial perfusion and sympathetic innervation of the heart.[19] Another PET-like quality, recently attributed to CZT-MPI is the feasibility to perform dynamic tomographic imaging, and quantify a myocardial perfusion reserve index, representing the ratio of peak myocardial blood flow to resting myocardial blood flow.[20,21] This measurement has the potential to increase the sensitivity of MPI in detecting extensive CAD when relative perfusion is normal due to balanced hypoperfusion, and reduced flow heterogeneity. A new PET-like performance of CZT technology is shown in the present study by Brodov et al, demonstrating the feasibility of measuring the EF reserve by short, successive acquisitions, starting 5 minutes after regadenoson injection, and detecting a negative, early EF reserve among ischemic patients, compared to a positive EF reserve among non-ischemic patients.

While several imaging modalities are currently available for evaluation of patients with CAD, nuclear cardiology continues to provide pertinent, useful bi-modal functional imaging of myocardial perfusion and LV function. Advanced CZT-based cameras provide fast, highly efficient SPECT imaging, superior to conventional technology, allowing improved assessment of ischemia and measurement of myocardial perfusion reserve on one hand, and assessment of LV functional reserve, on the other hand. Continuous efforts to improve the performance of the CZT detector units themselves are being made. Higher efficiency with faster processing capability of the gamma photons will improve the detection of dynamic changes in myocardial perfusion and function in response to stress, and will increase the diagnostic accuracy and improve risk assessment of patients with CAD.

Disclosure

Tali Sharir, Boris Brodkin have no conflict of interest. Gil Kovalski is employed by GE Healthcare.

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