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CARDIAC NUCLEAR IMAGING (A CUOCOLO AND M PETRETTA, SECTION EDITORS)

Stress Protocol and Myocardial Perfusion Imaging Accuracy

Alessia Gimelli[1] · Riccardo Liga[2]

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Abstract

Purpose of Review To evaluate the most recent evolutions in the field of single photon emission computed tomography (SPECT) nuclear cardiac imaging (NCI), particularly regarding the influence of stress protocol specifics on test accuracy.

Recent Findings The substantial improvement in both software and hardware SPECT settings may allow a drastic redefinition of the acquisition parameters, with a radical reduction of scanning time. Moreover, recent evidence has identified novel (contra)-indications to the different cardiac stressors, defining the categories of patients in which a specific stressor is most appropriate.

Summary Whilst exercise stress is favoured in the majority of patients submitted to SPECT NCI, in patients with atrial fibrillation or diabetes mellitus, a vasodilator stress may be preferred because of a significantly higher specificity. Moreover, the use of non-perfusion variables, such as post-stress diastolic left ventricular parameters or eccentricity index, is favoured to increase the accuracy of SPECT imaging. Finally, the quantification of myocardial blood flow through dynamic scans with cadmium-zinc-telluride cameras is gaining its way in clinical practice, possibly further increasing NCI accuracy in the most difficult patients.

Keywords CZT · Exercise stress · Pharmacological stress · SPECT · Diabetes mellitus · Atrial fibrillation

Introduction

Nuclear cardiac imaging (NCI) with single photon emission computed tomography (SPECT) is one of the oldest non-invasive cardiac imaging tests, still representing probably the most widely trusted modality for the evaluation of patients with suspect or known coronary artery disease (CAD). In fact, SPECT NCI is characterised by an excellent overall accuracy in unmasking the presence of significant CAD and in quantifying myocardial ischaemic burden [1], thus allowing the implementation of tailored therapeutic strategies aiming at improving patient's quality of life and possibly prognosis [2].

Among the major advantages of SPECT imaging, the most clinically relevant is probably its versatility. NCI can be coupled with any of the currently available stressors (i.e. exercise, vasodilators, and dobutamine), allowing evaluation of myocardial ischaemic burden in almost every category of patients [3]. Apart from the evaluation of regional myocardial perfusion heterogeneity, modern cardiac SPECT imaging can also allow the assessment of additional myocardial functional and structural parameters (i.e. diastolic function, transient ischaemic dilation (TID), and eccentricity) that may further refine its diagnostic and prognostic abilities [4–6]. Moreover, NCI has seen recently a major improvement in the hardware technology, represented by the introduction of dedicated cardiac cameras equipped with cadmium-zinc-telluride (CZT) detectors, allowing significant improvement of the photon sensitivity and spatial resolution of traditional SPECT devices, whilst reducing consistently both the radiation burden and acquisition times [7]. This recent revolution in the SPECT technology has been instrumental for a further improvement in the overall diagnostic abilities of the technology, whilst also allowing innovative applications of this methodology, such has myocardial blood flow (MBF) quantification [8•]. As a matter of fact, initial evidence has demonstrated the feasibility of dynamic CZT acquisitions, enabling the computation of regional MBF and myocardial flow reserve (MFR) in a PET-like fashion [8•, 9•].

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✉ Alessia Gimelli
gimelli@ftgm.it

Riccardo Liga
riccardo.liga@gmail.com

[1] Fondazione Toscana Gabriele Monasterio, Via Moruzzi, 1, 56124 Pisa, Italy

[2] Dipartimento di Patologia Chirurgica, Molecolare e dell'Area Critica, Università di Pisa, Pisa, Italy

However, despite these advancements, a number of questions regarding the interaction between both stress and acquisition protocols and SPECT accuracy remain, particularly when specific populations of patients are taken into account (i.e. diabetes, arrhythmias, and multivessel CAD).

To this purpose, the present review will summarise the most recent evidence on the subject, describing the advantages and limitations of the key imaging protocols of modern SPECT imaging.

Choosing the Stress Modality: Is Exercise Still the Reference Standard?

When NCI is delivered, the choice of the specific stress-test that should be performed in a particular patient is probably the most relevant aspect of the overall clinical reasoning, depending on the features of the reported symptoms (i.e. chest pain at rest or during stress), as well as on the characteristics of the patient (i.e. body habitus, ability to exercise, and comorbidities) [3]. In this context, if asked on which would be the most appropriate cardiac stress-test in the majority of patients submitted to SPECT NCI, the greatest majority of the cardiologists would probably answer exercise. As a matter of fact, exercise stress SPECT cardiac imaging allows the unique evaluation of both left ventricular (LV) perfusion and functional parameters during conditions of maximal cardiac energy expenditure, entailing the combined assessment of relevant measures of patients' global cardio-respiratory fitness and effort tolerance, which may further refine the overall prognostic abilities of the methodology [3]. Several investigations have confirmed repeatedly that a normal exercise stress SPECT may risk-stratify accurately patients with suspected or known CAD, with a predicted < 1% annualised event rate for major cardiac events [10]. On the contrary, pharmacological stress studies, even when normal, appear to be associated with a considerably lower prognostic ability and an overall higher long-term event rate, possibly as a result of the generally higher age and more extensive comorbidities of patients undergoing pharmacological stress test [11].

Despite the possible superiority of exercise over pharmacological stress test, a relevant proportion of patients submitted to SPECT NCI have significant exclusion criteria for the former stress modality (i.e. non-interpretable ECG or unable to exercise sufficiently), still needing to undergo a pharmacological stress evaluation.

In this respect, a recent study evaluating the impact of the different stress test modalities on the diagnostic ability of cardiac CZT imaging has excluded the presence of clinically relevant differences in the abilities of exercise and pharmacological stress test in unmasking the presence of significant CAD, with an overall similar accuracy of the two stress modalities both on per-patient (area under curve, AUC 0.76 vs 0.78, respectively; *P*=NS) and per-vessel basis (AUC, 0.78 vs 0.76, respectively; *P*=NS) [1]. Interestingly, exercise stress CZT maintained an appropriate diagnostic accuracy even in the case of sub-maximal exercise stress tests, as long as > 75% of the predicted maximal heart rate could be reached [1]. These findings are coupled by previous evidences that demonstrate clearly how the prognostic ability of exercise stress SPECT is maintained even in patients with impaired effort tolerance, suggesting the possible additive relevance of non-perfusion-related variables [11]. Accordingly, a number of data would seem to extend the indications for exercise stress SPECT, limiting the use of pharmacological stress agents only in those with relative contraindications to exercise or severely impaired effort tolerance. Recent evidences have further complicated this scenario, suggesting that some additional variables should be taken into account before choosing the most appropriate stress modality for the single patient that is submitted to cardiac SPECT. As a matter of fact, it has been shown that in at least two relevant categories of patients—namely those with atrial fibrillation and diabetes mellitus—a pharmacological stress agent, as represented by a coronary vasodilator (i.e. adenosine, dipyridamole, or regadenoson), would be preferable over exercise stress in order to maximise the diagnostic ability of cardiac perfusion SPECT imaging [12, 13•]. Specifically, the presence of atrial fibrillation may profoundly diminish the diagnostic ability of cardiac SPECT imaging in detecting significant CAD, with ≈ 10% reduction in the global accuracy. This effect was only apparent in the case of an exercise stress test, whilst disappeared in patients submitted to vasodilator stress, mainly because patients with atrial fibrillation undergoing exercise stress attained a significantly lower exercise time and overall cardiac workload than those in sinus rhythm, resulting in a consistently lower specificity in detecting significant CAD (54% vs 80%, $P = 0.016$) [13•].

The evaluation of the possible interaction between the presence of diabetes mellitus and the diagnostic accuracy of cardiac SPECT imaging dates back decades, with initial evidence confirming the elevated diagnostic power of NCI also in this category of patients [14]. However, a recent report has shown that cardiac SPECT imaging has a significantly lower specificity in patients with diabetes mellitus than in controls when an exercise stress- test is adopted, resulting in a lower accuracy (AUC, 0.70 vs 0.79; $P = 0.04$). Interestingly, no such difference was apparent in the case of vasodilator stress SPECT, suggesting that this stressor could be preferable in this clinical setting [12]. This finding could be related by the higher prevalence of obesity in patients with diabetes, resulting in a significantly lower exercise tolerance than in non-diabetic patients. In diabetic patients, cardiac SPECT imaging maintains the ability to further risk-stratify patients, adding relevant prognostic information over traditional clinical and functional variables.

Standard Versus Fast Acquisition Protocol: How Fast in the Era of CZT Cameras

SPECT NCI offers the chance for an automated evaluation of regional myocardial perfusion, allowing the semi-quantitative assessment of the presence and distribution of the ischaemic burden. However, despite these features, some still relevant limitations of the methodology make frequently the clinicians favour other non-invasive imaging modalities. Above all, the lengthiness of the imaging protocol that has typically characterised SPECT scans has been identified as one of the most relevant drawbacks. Recent improvements in the hardware and software settings have allowed to address this limitation, making SPECT NCI as fast as other cardiac imaging modality, whilst preserving, if not increasing, its overall diagnostic abilities [15, 16].

The introduction of dedicated CZT cardiac devices has allowed a radical reduction of the acquisition times, down to 4-to-6 min per scan, maintaining the global image quality whilst increasing patients' tolerability. Despite this reduction of the acquisition times, the overall duration of a SPECT scan is mainly determined by the waiting intervals (up to 60 min) between the injection of the radiopharmaceutical and the acquisition, in order to allow the reduction of the background and subdiaphragmatic activity. Reports on the feasibility to reduce those technical time-intervals have been discordant, with some early evidence suggesting that an "early acquisition" protocol (i.e. within 15 min from the end of the stress) would preserve image quality whilst further increasing the sensitivity in detecting significant CAD [17•]. This latter aspect is of particular relevance since a faster image acquisition protocol, with a substantial reduction of the interval between the end of the stress test and SPECT scan, would allow a more favourable timing of the acquisition with respect to the ischaemic event, possibly increasing the ability to detect more subtle alterations of myocardial perfusion, as signs of transient myocardial ischemia that could have disappeared on later scans [18]. These findings were confirmed recently using a dedicated cardiac CZT camera, demonstrating that early acquisitions (starting 3.5 to 5 min after tracer injection) were adequate in the majority of patients, possibly helping to avoid some of the most common image artefacts related to extra-cardiac uptake or even, at least theoretically, to radiotracer's redistribution [19]. The combination of early acquisition protocols together with a reduced scanning time, as almost always possible with the use of CZT cameras, is increasing the competitiveness of SPECT NCI, making it a valid alternative to any other non-invasive imaging modality in a wide variety of patients and clinical settings.

Additional Parameters for the Evaluation of Patients with Ischaemic Heart Disease

Whilst the accurate evaluation of regional myocardial perfusion heterogeneity is the backbone of cardiac SPECT imaging, a number of additional cardiac structural and functional variables may be also assessed during the same imaging session, providing additional information that may both increase the diagnostic power of the methodology and increase the overall prognostic power of the imaging modality [5]. Among those functional variables, the quantification of LV diastolic parameters has recently gained relevance in the field of NCI, particularly in the setting of ischaemic patients. In fact, diastolic dysfunction may appear before stress-induced alteration of myocardial contractile function, representing an earlier step of the ischaemic cascade [4, 20]. In this setting, the peak filling rate (PFR) and the time to PFR represent the two most validated parameters for the evaluation of LV relaxation, with the former playing a central role in the recent literature on the topic [20, 21]. The theory behind this concept is that, whilst LV diastolic function ameliorates during stress in healthy patients, as a sign of a better cardiac pumping capacity, the same is not true in the setting of CAD, a condition that associates with the development of stress-induced LV diastolic dysfunction. In this respect, alterations of the SPECT-derived PFR during stress are both sensitive and specific markers of CAD, being already apparent in patients with non-obstructive disease and increasing linearly in relationship with CAD burden, overwhelming the diagnostic ability of any other LV functional variable (i.e. LV ejection fraction) [21]. Regarding cardiac structural analysis, modern SPECT imaging offers the chance to obtain relevant information on LV geometry both at rest and after stress. In this setting, two parameters—namely transient ischaemic dilation (TID) and eccentricity index (EI)—have demonstrated their additional value in the evaluation of ischaemic patients, implementing perfusion analysis and possibly increasing the overall diagnostic accuracy in detecting CAD [22•]. TID of the LV during stress SPECT has been associated with severe and extensive CAD, providing incremental diagnostic information over standard myocardial perfusion analysis with particular regard to patients with diabetes mellitus, where TID assessment may provide relevant, independent, long-term prognostic information [23].

If TID is a sign of dynamic, ischemia-related, LV structural changes, the EI is a pure measure of static LV three-dimensional shape, with relevant prognostic implications particularly in patients with depressed ejection fraction. More recently, a lower post-stress EI, representing a more spherical LV, has been associated independently with the presence of CAD, predicting specifically the presence of multivessel disease, see Fig. 1 [24]. Interestingly, this association was only apparent in patients submitted to exercise stress test,

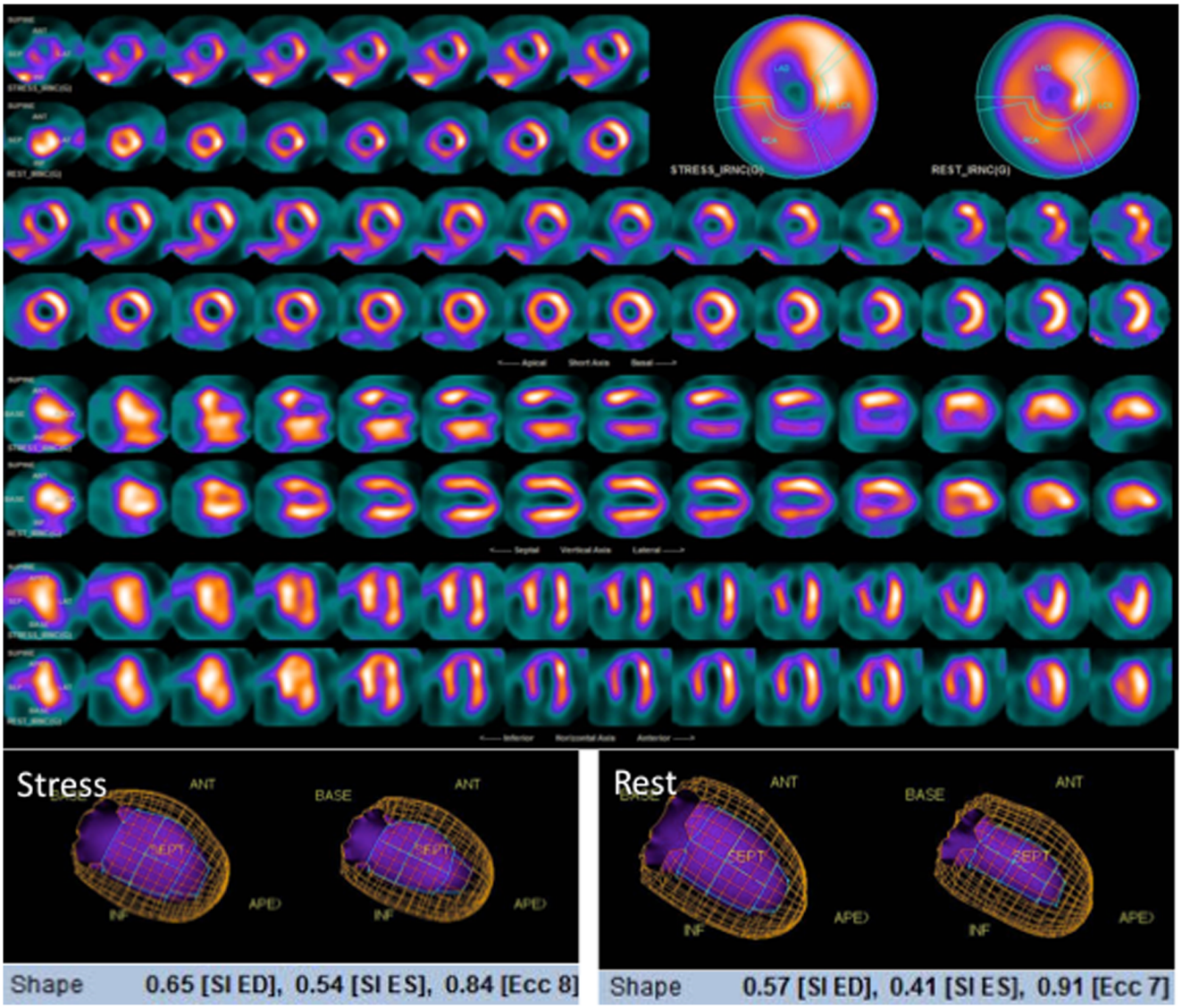

Fig. 1 A 65-year-old lady with multiple risk factors and effort dyspnoea. She was submitted to single day stress rest CZT low dose scan (4.1 mSv in total). Perfusion images indicates the presence of multivessel transitory perfusion abnormalities. The analysis of shape demonstrates the presence of an important change of ventricular geometry after stress and at rest

suggesting the inability of vasodilators to induce the sufficient amount of ischemia that may cause transient LV structural remodelling and dysfunction.

In the setting of vasodilator stress, the assessment of the magnitude of stress-related patient's chronotropic competence has been suggested as a relevant additional variable that may both impact the diagnostic accuracy of the exam and even the overall prognostic power of the test. In fact, in patients with a blunted chronotropic competence to vasodilator—i.e. characterised by a less pronounced increase of heart rate—SPECT imaging is characterised by a relatively lower accuracy than in those with preserved heart rate reserve, also associating with unfavourable patient's long-term survival [25, 26].

These data could suggest a better protocol selection in patients with chronotropic incompetence to vasodilator stress, in whom a short course of isometric exercise (i.e. handgrip or low-level exercise) might improve SPECT NCI sensitivity by increasing the heart rate.

MBF Quantification with SPECT: the Future Is Now

The standard semi-quantitative approach for the evaluation of SPECT myocardial perfusion images remains a valid method for unmasking the presence of significant coronary stenosis in the majority of patients. However, in the case of multivessel CAD, it often reveals only the coronary territory subtended by the vessel with the most hemodynamically significant lesion, possibly missing the presence of coronary luminal narrowing

elsewhere. This limitation may be the result of the presence of the so-called balanced ischemia, a condition determined by the fact that in the presence of a diffuse reduction of myocardial perfusion reserve (MPR), regional myocardial perfusion heterogeneity is decreased, hence reducing the diagnostic ability of semi-quantitative SPECT analysis [27]. In this context, absolute quantification of MPR has been proposed as the most obvious approach to overcome this drawback. However, traditional SPECT cameras are largely unsuitable to this purpose because of the limited detector sensitivity and temporal resolution, leading to roll-off phenomenon at higher flow values. The introduction of CZT cameras allows cardiac imaging in a non-rotating list-mode acquisition, making it possible to derive time–activity curves of radiotracer distribution in the myocardium and in the blood pool, enabling absolute MBF quantification [7, 8•, 9•]. Accordingly, the feasibility of the evaluation of MPR through dynamic CZT imaging has been recently demonstrated in some proof-of-concept studies, showing that estimates of regional MPR obtained with this technology seem to match well the results of PET imaging and discriminate readily the presence of significant CAD, possibly helping in the characterisation of patients with globally reduced myocardial perfusion (i.e. multivessel CAD or microvascular disease) [8•, 28•]. Nevertheless, the obvious drawbacks of ^{99m}Tc-based radiotracers, characterised by a limited extraction fraction from the blood pool that is also variable depending on the flow-rate, limit the absolute quantification of myocardial blood flow and hence the accurate estimation of MPR values on CZT, which are classically inferior to those obtained on PET imaging. Whether this latter aspect will somehow influence the diffusion of dynamic CZT imaging in clinical practice is still largely unknown.

Conclusions

The evolution of cardiac SPECT imaging that has taken place in the last decade has been characterised by radical changes in both hardware and software settings. Specifically, the introduction of dedicated CZT cardiac cameras has allowed consistent reduction of injected radiotracer activity and acquisition time, decreasing the overall length of the scanning protocol whilst further improving the diagnostic accuracy of the methodology and possibly giving the chance to quantify absolute MPR, improving the impact of SPECT results for clinical decision making. In this context, evidence has been accumulating on the importance of the correct definition of the best imaging protocol for the specific patient, particularly regarding stress-agent selection. Accordingly, whilst an exercise stress test, even if modestly sub-maximal may be preferred in the majority of patients, in some relevant categories of individuals—such as those with diabetes mellitus and atrial fibrillation—a vasodilator stressor may be preferred.

Compliance with Ethical Standards

Conflict of Interest Alessia Gimelli and Riccardo Liga declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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