Title

A combined static-dynamic single-dose imaging protocol to compare quantitative dynamic SPECT with static conventional SPECT

Journal

Journal of Nuclear Cardiology, 26(3)

ISSN

1071-3581

Authors

Sciammarella, Maria
Shrestha, Uttam M
Seo, Youngho
et al.

Publication Date

2019-06-01

DOI

10.1007/s12350-017-1016-7

Peer reviewed

A combined static-dynamic single-dose imaging protocol to compare quantitative dynamic SPECT with static conventional SPECT

Maria Sciammarella, MD,[a] Uttam M. Shrestha, PhD,[b] Youngho Seo, PhD,[b] Grant T. Gullberg, PhD,[b] and Elias H. Botvinick, MD[a,b]

[a] Division of Cardiology, Department of Medicine, University of California, San Francisco, CA
[b] Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA

Received Feb 3, 2017; accepted Jul 11, 2017
doi:10.1007/s12350-017-1016-7

Background. **SPECT myocardial perfusion imaging (MPI) is a clinical mainstay that is typically performed with static imaging protocols and visually or semi-quantitatively assessed for perfusion defects based upon the relative intensity of myocardial regions. Dynamic cardiac SPECT presents a new imaging technique based on time-varying information of radiotracer distribution, which permits the evaluation of regional myocardial blood flow (MBF) and coronary flow reserve (CFR). In this work, a preliminary feasibility study was conducted in a small patient sample designed to implement a unique combined static-dynamic single-dose one-day visit imaging protocol to compare quantitative dynamic SPECT with static conventional SPECT for improving the diagnosis of coronary artery disease (CAD).**

Methods. **Fifteen patients (11 males, four females, mean age 71 ± 9 years) were enrolled for a combined dynamic and static SPECT (Infinia Hawkeye 4, GE Healthcare) imaging protocol with a single dose of ^{99m}Tc-tetrofosmin administered at rest and a single dose administered at stress in a one-day visit. Out of 15 patients, eleven had selective coronary angiography (SCA), 8 within 6 months and the rest within 24 months of SPECT imaging, without intervening symptoms or interventions. The extent and severity of perfusion defects in each myocardial region was graded visually. Dynamically acquired data were also used to estimate the MBF and CFR. Both visually graded images and estimated CFR were tested against SCA as a reference to evaluate the validity of the methods.**

Results. **Overall, conventional static SPECT was normal in ten patients and abnormal in five patients, dynamic SPECT was normal in 12 patients and abnormal in three patients, and CFR from dynamic SPECT was normal in nine patients and abnormal in six patients. Among those 11 patients with SCA, conventional SPECT was normal in 5, 3 with documented CAD on SCA with an overall accuracy of 64%, sensitivity of 40% and specificity of 83%. Dynamic SPECT image analysis also produced a similar accuracy, sensitivity, and specificity. CFR was normal in 6, each with CAD on SCA with an overall accuracy of 91%, sensitivity of 80%, and specificity of 100%. The mean CFR was significantly lower for SCA detected abnormal than for normal patients (3.86±1.06 vs 1.94±0. 0.67, $P < 0.001$).**

Conclusions. **The visually assessed image findings in static and dynamic SPECT are subjective, and may not reflect direct physiologic measures of coronary lesion based on SCA. The CFR measured with dynamic SPECT is fully objective, with better sensitivity and specificity, available only with the data generated from the dynamic SPECT method. (J Nucl Cardiol 2017)**

Key Words: Dynamic SPECT • Clinical SPECT/CT • Selective coronary angiograph • ^{99m}Tc-Tetrofosmin • Coronary flow reserve

Reprint requests: Uttam M. Shrestha, PhD, Department of Radiology and Biomedical Imaging, University of California, 185 Berry St., Suite 350, San Francisco, CA 94143-0946; *uttam.shrestha@ucsf.edu*

1071-3581/$34.00

Published online: 03 August 2017

Abbreviations	
SCA	Selective Coronary angiography
CABG	Coronary bypass graft surgery
CAD	Coronary artery disease
CFR	Coronary flow reserve
MBF	Myocardial blood flow
MPI	Myocardial perfusion imaging
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
SPECT	Single-photon emission computed tomography
CT	Computed Tomography

INTRODUCTION

Myocardial perfusion imaging (MPI) using single-photon emission computed tomography (SPECT) has been a critical tool in the diagnosis of coronary artery disease (CAD) and related disorders.[1] As currently applied, clinical cardiac SPECT acquired with a static imaging protocol, assesses perfusion defects by visual inspection and automated semi-quantitative analysis, of the pattern of relative regional intensity of radioactivity localized in the myocardium in proportion to regional myocardial blood flow (MBF).[2,3] Visual assessment has been supported by semi-quantitative methods which compare these patterns to the normal, gender-based intensity distribution and attenuation correction (AC) algorithms which seek to correct for this most common artifacts.[4] In contrast, dynamic imaging captures the temporal dynamics of the extraction and localization of the radiotracer, and thus can generate additional time-varying information such as absolute regional MBF and coronary flow reserve (CFR).[5–12]

Besides providing the quantitative value of regional flow, dynamic cardiac imaging provides 4D image sets—3D volume and 1D time—so that unlike static clinical 3D images, one can identify and select the optimal time frame that would give a high-contrast image to enhance the most accurate visual diagnosis. Since the dynamic SPECT method measures absolute MBF and CFR, not simply relative values, the method could unveil the presence of three-vessel CAD otherwise shrouded in the pattern of relative symmetry.[5,13] Such added abilities would further increase the diagnostic capabilities of the method and, so likely, also its prognostic value.

Despite the potential of clinical importance of MBF and CFR, they are still rarely used in the standard clinical practice because of a number of reasons. As of now, with suitable radiotracers, PET has been shown to allow a relatively accurate quantification of regional MBF.[14–17] For SPECT, there is a lack of clear methodology. A major hurdle could be the modification of currently available standard clinical tools that perform flow quantification as a part of standard SPECT MPI scans.[18–20]

The main objective of this preliminary feasibility study was to demonstrate the viability of a single-dose combined dynamic and static SPECT MPI protocol using a commonly available gamma camera with ^{99m}Tc-tetrofosmin, and to compare SPECT MPI data acquired dynamically with that acquired after the radiotracer stabilizes temporally in the myocardium at rest and with vasodilator pharmacologic stress. In order to ensure the most accurate comparison, a single combined imaging protocol was applied; each rest and stress static and dynamic acquisition was performed with the same, single injected radionuclide dose with a common pharmacological stress intervention for both static and dynamic imaging studies. Our previously developed method[5] of calculating CFR was used to compare a quantitative to a visual approach in the assessment of disease.

METHODS

Patient Population

The study included 15 patients (ten males and five females) among those participating in our ongoing dynamic cardiac SPECT study who were willing to have a dynamic followed by a conventional cardiac SPECT study both at rest and after pharmacologic stress. The study was approved by the Institutional Review Board of the University of California, San Francisco (UCSF). Informed verbal consent was obtained from each subject with the initial patient contact, and full written informed consent was obtained, after fully educating each subject about the possible risks and benefits of their participation prior to the initial scan. In each patient, the cardiac history and other pertinent medical history were reviewed including a past history of hypertension, hyperlipidemia and smoking. A lipid profile was analyzed and medications were reviewed with special note taken of statins, beta-blockers, calcium-channel-blockers, nitrates, diuretics, and other anti-hypertensive therapy. Clinical indicators such as blood pressure (BP), heart rate (HR), and left ventricular ejection fraction (LVEF) were recorded for each patient at rest and with stress.

Out of 15 patients, eleven had selective coronary angiography (SCA), eight within 6 months and the rest within 24 months of SPECT imaging, without intervening symptoms or interventions. Three patients had previously undergone percutaneous coronary intervention (PCI) without remnant stenosis while one patient had prior coronary bypass graft

surgery (CABG) with all grafts open with full revascularization. For the purpose of this study, those patients with successful PCI and complete revascularization of all pathophysiologically stenotic lesions at CABG were considered to have normal coronary anatomy.

Combined Dynamic and Static Clinical Cardiac SPECT/CT Protocol

A SPECT/CT scanner (Infinia Hawkeye 4, GE Healthcare) was used for all studies. Prior to the study, all patients fasted for at least 4 hours and refrained from caffeine-containing beverages for 24 hours.

At the time of the study, none of the patients was taking any cardiotropic or antihypertensive drug. A low-dose/high-dose rest/pharmacologic-induced-stress protocol was implemented in a single day visit. A single standard rest and a single standard stress radionuclide dose was administered and utilized for both dynamic and conventional static SPECT studies. There was no added radionuclide dose or radiation exposure compared to the standard clinical protocol.

Imaging always began with a dynamic study followed by the static clinical study, first at rest, followed by pharmacologic stress. Figure 1 shows the timing of the combined dynamic/static rest/stress protocol. The dynamic imaging protocol consisted of a 20 minute continuous camera rotation with the detector head in H-mode configuration while the static imaging protocol consisted of a standard 15 minute step-and-shoot 180° static acquisition with the detector head in L-mode configuration. CT images (helical, 5 mm slice thickness, 80 slices) were acquired immediately after the SPECT acquisitions for attenuation correction and localization.

The dynamic acquisition began immediately prior to the radiotracer injection, with patients lying in the supine position. Once the scanner heads began rotating, each patient received a bolus injection (10–20 seconds duration) of approximately 370 MBq (10 mCi) of ^{99m}Tc-tetrofosmin (140 keV) (Myoview; GE Healthcare) at rest.

With stress, patients were given a 0.4 mg IV bolus injection of regadenoson (Lexiscan; Astellas Pharma, Inc.), followed by approximately 937 MBq (25 mCi) of ^{99m}Tc-tetrofosmin (flushed with a 10 mL saline solution) approximately 60–90 seconds later. If there were persistent regadenoson-related side effects, patients received 25–50 mg of aminophylline, an adenosine antagonist, approximately 5–7 minutes after regadenoson injection.

The heart rate, blood pressure, and twelve-lead ECG were recorded at baseline and monitored continuously after regadenoson administration.

Image Reconstruction

The dynamic SPECT data for each patient were reconstructed using the standard 4-dimensional maximum likelihood expectation maximization (ML-EM) algorithm[21] applicable to spatiotemporal image reconstruction in emission tomography, a software package developed by LBNL/UCSF for the continuous rotation dual-head detector acquisition.[12,22,23] The object space was voxelized in a dimension of 128^3 with each voxel of physical volume of 4.4 mm^3. The CT map served for both body contouring and implementation of attenuation correction. Since the data were distributed over a single energy window with the photo peak of 140 keV, scattering correction was not applied. However, collimator response and partial volume correction were modeled explicitly during

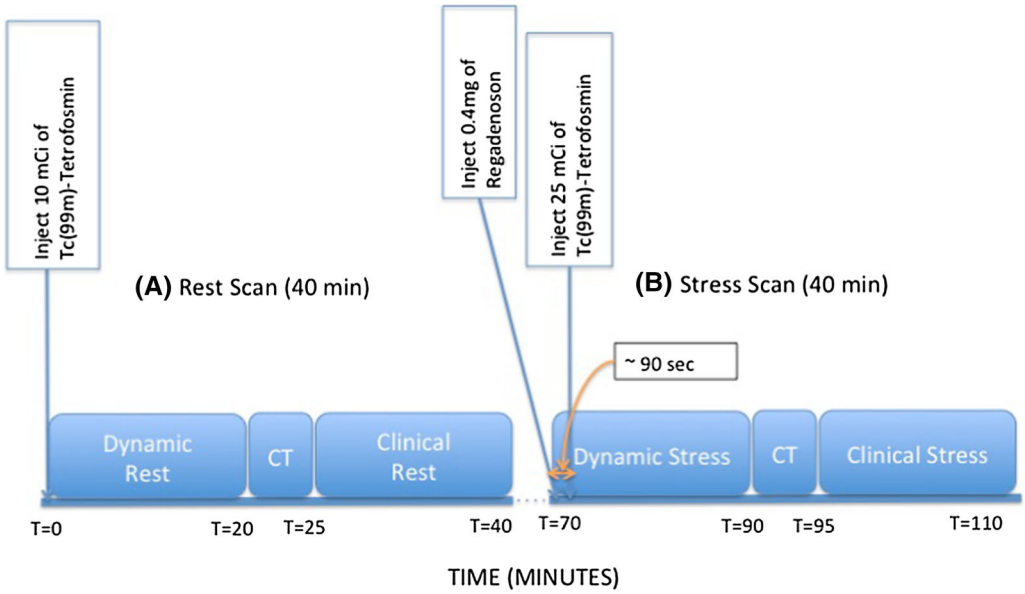

Figure 1. Timing for the combined dynamic and static cardiac SPECT/CT rest/stress imaging protocol with low-dose/high-dose ^{99m}Tc-tetrofosmin.

iterative image reconstruction by incorporating the point-spread-function (PSF) in the system matrix. The time series, i.e., the temporal information of the tracer activity at each voxel, were extracted every 5 seconds from the reconstructed images.

The clinical images were reconstructed using the standard vendor provided ordered subsets expectation maximization (OS-EM) algorithm.[24] Both dynamic and static image reconstruction methods employed the PSF modeling and were attenuation corrected.

For visual comparison, the image from the clinical static acquisition was compared with the optimum dynamic image selected from the 5 second sequence of 3D dynamic SPECT images. The optimal dynamic SPECT image was determined by the ratio of the myocardium to liver/gut activity after tracer injection. In our study, significant blood clearance occurred around 5 minutes after the tracer injection as the visibility of the myocardium builds up with no significant blood contamination. Early uptake contamination from adjacent organs was not observed as the uptake and washout occur at a later time. Image blurring due to cardiac and respiratory motion was neglected. Cross-contamination due to blood spillover between myocardium and left and right ventricles was corrected during fitting of the time activity curves (TACs) to compartment models. Clear delineation of the myocardium with optimum contrast was obtained between 8 and 12 minutes after injection. Therefore, delineated dynamic SPECT images at approximately between 10 and 12 minutes after the tracer injection were used for the comparison between the conventional SPECT image and the images from dynamic SPECT.

Estimation of MBF and CFR

Data acquired dynamically were used to estimate the myocardial blood flow (MBF). Myocardial blood flows were calculated by modeling the extraction fraction as described in our previous work on quantitation of MBF with ^{99m}Tc-tetrofosmin.[5] The correspondence between flow values in the coronary vasculature (LAD, RCA, and LCX) with myocardial segments defined by the standardized myocardial segmentation and nomenclature were derived.[23] The coronary flow reserve, CFR, was defined as the ratio of stress to rest MBF values. The CFR values greater than 2.0 in each coronary vascular region were taken as normal, and that less than 2.0 was taken as abnormal for drawing statistical inferences.[25]

Coronary Angiography

Eleven patients also underwent selective coronary angiography (SCA) for the evaluation of clinical indications of vascular stenotic lesions. The procedure was performed in the standard fashion in multiple orthogonal views to evaluate the percent stenosis in major coronary arteries. The degree of stenosis of the coronary arteries was visually estimated as a percentage of the normal segment preceding the stenosis. In these patients, significant coronary stenosis was defined as 70% narrowing of the lumen diameter of a native coronary artery in the left main (LM), left anterior descending (LAD), left circumflex (LCX), or right coronary artery (RCA) and its main branch vessels.[26] All vessels with coronary artery bypass grafting (CABG) were considered patent.

Statistical Analysis

All estimated values were expressed as mean ± SD. Median and quartile values were also calculated. *P*-values were calculated using two-tailed *t*-test to draw statistical significance. Any *P*-value less than 0.05 was considered statistically significant.

All statistical calculations were performed using the *open-source statistical* package R (http://www.R-project.org/).

RESULTS

Clinical characteristics of the patients were reviewed and summarized in Table 1. Among the 11 males and four females enlisted, the mean age was 71 ± 9 years (range 47 to 84). Thirteen patients had a history of and were being treated for hypertension, 12 for hyperlipidemia and six for diabetes mellitus. Six patients had a previously documented history of CAD and 11 had coronary angiography before or after dynamic cardiac SPECT study without any intervening events. Five patients among those with known coronary anatomy had normal coronary arteries while the remaining six patients had significant CAD on SCA.

The summary of the individual patient results for conventional static SPECT, dynamic SPECT, SCA, and CFR calculated from dynamic SPECT data are tabulated in Table 2. Two patients had non-ischemic cardiomyopathy one with congestive cardiomyopathy and the other induced by LBBB. One patient had both SPECT and PET MPI within 3 months. The patient had normal SPECT but abnormal PET. So, it was treated as normal in our calculation.

Table 1. Clinical characteristics of study patients

Characteristics	Values
Age	71 ± 9 years
Gender	11 Male, 4 Female
Hypertension	13
Dyslipidemia	12
Diabetes	6
PCI	3
CABG	1
LVEF*	12(N), 3(A)
History of CAD	6

* LVEF above 50% were considered normal (N)

Conventional static SPECT was normal in ten patients and abnormal in five patients. Among those 11 patients with SCA, conventional SPECT was normal in 8, 3 with documented CAD on SCA and abnormal in 2, with an overall accuracy of 64% (7/11), sensitivity of 40% (2/5), and specificity of 83% (5/6).

The readings from dynamic SPECT were normal in 11 patients and abnormal in four patients. Among those 11 patients with SCA, images from dynamic SPECT were normal in 9, 2 with CAD documented on SCA with an overall accuracy of 64% (7/11), sensitivity of 40% (2/5) and specificity of 100% (6/6). All three patients with normal images from dynamic SPECT had single-vessel disease in SCA.

The CFR measured from dynamic SPECT was normal in 9 patients and abnormal in 6 patients. Among those patients with SCA, CFR was normal in 6, 1 with CAD on SCA and abnormal in 5 with an overall accuracy of 91% (10/11), sensitivity of 80% (4/5) and specificity of 100% (6/6). Also, regional CFR abnormalities agreed with the distribution of CAD, but in one patient with single vessel disease, demonstrated abnormal CFR in the regions of all three coronary arteries. CFR was also widely abnormal in association with normal anatomic coronary arteries in a patient with a congestive non-coronary cardiomyopathy. However, CFR measurement maintained its specificity and was generally normal in diabetic and hypertensive patients without CAD.

In Figure 2, we show the distribution of regional CFR measured with dynamic cardiac SPECT in a group of patients who had SCA. A coronary stenosis was considered significant when the narrowing of the lumen diameter of a native coronary artery was greater than 70%. Out of 30 vessels evaluated, 24 were normal and 6 were abnormal. The normal and abnormal mean CFR were, respectively, 3.86 ± 1.06 and 1.94 ± 0.67 ($P < 0.001$). Both mean and median CFR were significantly lower for abnormal than that for the normal vessels (Table 3).

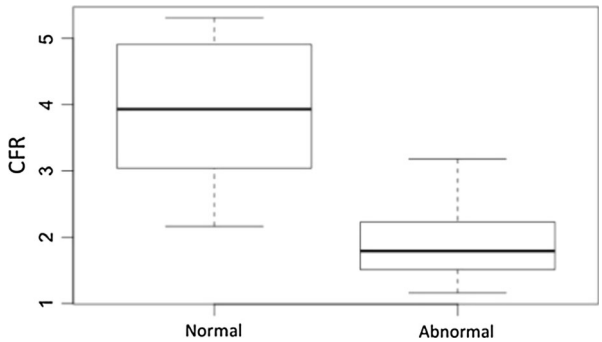

Figure 2. Statistical comparison between normal and abnormal CFR values measured with dynamic cardiac SPECT in a group of patients who had SCA. In these patients, coronary stenosis was considered significant when the narrowing of the lumen diameter of a native coronary artery was greater than 70%. Altogether 30 vessels (six obstructive, 24 non-obstructive) corresponding to 10 patients were evaluated. The CFR mean value was significantly lower for abnormal than that for the normal group (Normal mean CFR = 3.86 ± 1.06, Abnormal Mean CFR = 1.94 ± 0.67, $P < 0.001$).

Table 2. Comparison between conventional, dynamic SPECT and CFR with SCA

Patient ID	Conv. SPECT	Dyn. SPECT	SCA	CFR
1	A (LCX)	N	N	N
2	A (LCX)	A (LCX)	A (LAD, LCX)	A (LCX)
3	N	N	N	N
4	N	N	N	N
5	N	N	-	N
6	N	N	N	N
7	A (LCX)	A (LCX)	A (LCX)	A (LCX)
8	N	N	N	N
9	N	N	N	N
10	N	N	-	N
11	N	N	A (LAD)	A (LAD, RCA)
12	A (LAD, LCX)*	A(LAD, LCX)	-	A (LAD, LCX)
13	N	N	A (LCX)	N
14	N**	N	A (LAD)	A (LAD)
15	A (LAD)***	A (LAD)	-	N

* Congestive cardiomyopathy; ** abnormal PET; *** (LBBB-induced cardiomyopathy)

Table 3. CFR summary statistics for normal ($n = 24$) and abnormal ($n = 6$) vessels

	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
Abnormal	1.153	1.512	1.79	1.944	2.229	3.179
Normal	2.165	3.074	3.932	3.865	4.879	5.314

DISCUSSION

This study applied a unique imaging protocol in which both a conventional and a dynamic SPECT MPI study were acquired with a single dose administered at rest and a single dose administered at stress to compare static and dynamic imaging approaches for assessing the presence and extent of CAD with pharmacologic stress. While dynamic PET MPI is a well-established method for measuring MBF and CFR, static SPECT MPI has been a standard and important clinical tool in the diagnosis and risk stratification of CAD.[1] The current SPECT MPI method analyzes static images to visually evaluate the distribution of perfusion defects and gives a semi-quantitative assessment of the extent and severity of coronary lesions. To improve quantitation of SPECT MPI, we developed a method for calculating CFR using dynamic cardiac SPECT with ^{99m}Tc-tetrofosmin, and in this study, we obtained an overall accuracy of 91% (10/11), sensitivity of 80% (4/5), and specificity of 100% (6/6) using SCA as a reference.

In spite of PET being used for quantification of MPI and for measuring MBF and CFR for the last two decades, it has not been routinely used worldwide due to limited availability of resources such as cyclotrons (for $^{13}NH_3$) and generators (for ^{82}Rb).[18] SPECT is the most commonly used MPI tool with over 7 million scans performed in the United States annually. A recent review showing the success of using PET/CT CFR measurements in the diagnosis of CAD has encouraged investigators to use the more commonly available SPECT instrumentation for quantifying MBF and CFR.[27] This motivates the need of improved SPECT methods to perform both visual assessment and flow quantification as part of standard MPI that would open up the possibility of much wider clinical application in the near future.

This preliminary feasibility study was conducted in a small patient sample designed to compare dynamic with static conventional SPECT MPI in the diagnosis of CAD. The main goal of the study was to assess the feasibility of developing a clinical protocol for a conventional SPECT camera that integrates dynamic and static SPECT with a single dose for rest and a single dose for stress without additional radiation burden. The unique combined static-dynamic single-dose imaging protocol was applied in a one-day visit in order to ensure the most accurate comparison between the two studies without any additional dose. Both visual inspection of static and dynamic images and quantitative estimation of flow using our previously developed method[5] were tested against selective coronary angiography (SCA) to find the validity of the methods.

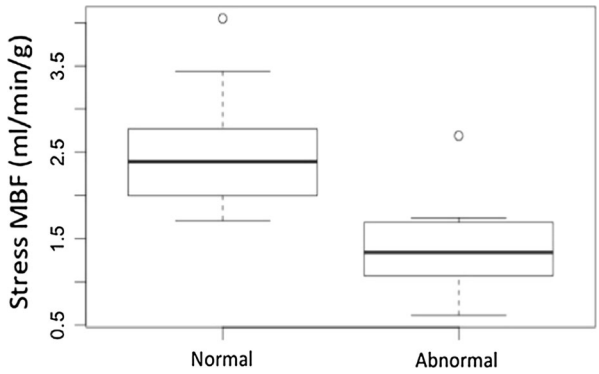

Figure 3. Statistical comparison between normal and abnormal stress MBF. The mean MBF was significantly lower for abnormal than that for the normal group (Normal mean MBF = 2.49 ± 0.61, abnormal mean MBF = 1.43 ± 0.62, $P < 0.001$). Altogether 30 vessels (six obstructive, 24 non-obstructive) were included.

The quantitative dynamic method could become complementary to static SPECT MPI in improving the quality of image and diagnostic accuracy. It has the ability to generate time-dependent hemodynamic parameters such as regional MBF and CFR that could provide increased sensitivity in identifying a number of abnormal coronary vascular regions.[13,28,29] This potential ability to identify more involved coronary vascular regions would aid diagnosis of multivessel CAD that is otherwise obscured in the homogeneous pattern of uniformly reduced coronary flow and flow reserve. Improved identification of the extent of CAD would then permit a more complete assessment of the ''ischemic burden'' and more accurate prognosis. Additionally, dynamic imaging permits the identification and selection of the optimal reconstruction time frame providing the image with the highest myocardial contrast that could optimize image reading and improve CAD diagnosis.

Quantification of myocardial blood flow (MBF) with SPECT has gained significant impetus with dozens of research publications each year. Our work not only

highlights the feasibility of the use of commonly available SPECT cameras and radiotracers for the estimation of MBF but also proposes a possible vertical integration of the method into clinical SPECT at almost no additional cost. It should be pointed out that our imaging protocol recognizes an important change in clinical practice for SPECT MPI that would be required for routine measurement of MBF at rest and stress; namely that dynamic imaging needs to start at the time of tracer injection, and the standard uptake interval of 30–45 min after tracer injection may not be needed or efficient for combined assessment of SPECT MPI and MBF.

There has been significant progress on the potential use of dynamic SPECT to calculate regional MBF and CFR using several different cameras, methods, and radiopharmaceuticals.[5,8–11,13,20,30–32] Conventional dual-head SPECT scanners have been used in an attempt to measure MBF,[10] coronary flow index (CFI),[33] and CFR.[5] Using SPECT for estimating MBF and CFR has not only inspired clinicians with its potential application but also has reintroduced the long-term discussion of the importance of correcting for the deleterious effects of the imaging physics when using this technology.[34] In the quest to advance the quantitative SPECT MPI method and technology, we recently proposed a method for estimating the extraction fraction of ^{99m}Tc-tetrofosmin in the myocardium in an effort to revitalize the possibility of using a commonly available conventional dual-head SPECT camera for the estimation of MBF and CFR.[5]

Among those patients with SCA, our study showed that the CFR measurement had the best correlation with the coronary anatomy. Interesting too, was the fact that although localization of disease using imaging and CFR correlated well with SCA, CFR sometimes identified abnormalities where there was no apparent flow limiting anatomic stenosis, suggesting abnormal microvascular function possibly due to endothelial dysfunction, rather than anatomic narrowing. This is seen in one patient studied with a non-ischemic cardiomyopathy who nonetheless demonstrated widespread abnormalities of CFR. Although patients with hypertension and diabetes mellitus may have altered vascular reactivity and thus entailed abnormal CFR despite normal coronary arteries, our study showed that the CFR measurement in some of these patients were abnormal, providing optimism that the method will maintain acceptable level of specificity for the functional abnormality related to CAD. In an effort to resolve the accuracy of findings on the remaining four patients, image readings for these patients were compared with the regional CFR findings, given its excellent agreement with SCA. Three out of the remaining four patients had normal CFR values.

It has been suggested that the absolute stress perfusion alone could be sufficient to detect hemodynamically significant CAD.[35] In Figure 3, we show stress MBF for angiographically normal and abnormal vessels (with 70% stenotic cutoff) that may also be used in the evaluation of significant CAD. The mean stress MBF value was significantly lower for abnormal than that for the normal (normal mean MBF = 2.49 ± 0.61, abnormal mean MBF = 1.43 ± 0. 0.62, $P < 0.001$). Such a 'stress only' protocol may allow shorter imaging time with less radiation burden.

There is expected to be differences in the dynamically and statically acquired images when using the conventional dual-headed SPECT camera, because of the different camera arrangements during acquisition and different data processing. In our work, the static acquisition was acquired in L-mode for 15 minutes when the activity was dynamically stable in the heart. Therefore, the projection views were consistent, whereas the dynamic acquisition was acquired in H-mode while the tracer was changing dynamically from projection to projection. L-mode would provide less statistics than the dynamic acquisition in H-mode but provide some advantage in consistency over time. The processing of the dynamic data also improves signal to noise by fitting the data over time. However, dynamic acquisitions could only be performed in H-mode with the detector heads retracted at full extent. This caused resolution loss compared to the static acquisition, but the PSF modeling improved this significantly. We found that dynamic SPECT produced the similar image quality as static SPECT when the selected image had optimal target to background ratio.

Although the dynamic SPECT acquisition uses conventional gamma camera detectors, it uses rapid continuous rotation (slip-ring gantry) and CT-based attenuation correction. Only a small fraction of installed SPECT cameras have both these capabilities. However, our protocol and data processing method can also be implemented with any camera that can perform rapid forward and backward acquisition or with any dedicated cardiac SPECT camera.

The sensitivity and specificity values with our conventional and dynamic SPECT image analysis were lower than currently reported numbers in literature.[4,36] This may be due to the small patient population ($n = 11$) where the sensitivity and specificity can fluctuate significantly with a small variation of patient number, i.e., a change of one patient would change the sensitivity by an addend of ten or more. Compared with SCA, both visually assessed conventional static and dynamic SPECT images demonstrated an inferior diagnostic accuracy. In addition to the small number of patients, the patient cohort heterogeneity could be an important factor for the lower sensitivity and specificity results. The study consisted of not only patients with

suspected or known CAD but also with other complications such as dyslipidemia, diabetes, and cardiomyopathy. The wider age range might have also affected the age-related hemodynamic factors due to wide variability in the hyperemic MBF in the older patient group.[37] There also was a prolonged temporal duration between SPECT imaging and SCA, though there were no clinically intervening events. Most patients with CAD in SCA also had single-vessel disease, a group known to relate to a lower diagnostic sensitivity by all non-invasive scintigraphic methods.[38]

LIMITATIONS

A significant limitation of this study was the small number of patients and their clinical heterogeneities. Due to the small patient population, we were unable to perform RCA analysis, which would provide a better evaluation of sensitivity and specificity and thus, the accuracy of our method. There also was a somewhat long duration (up to 2 years) between SPECT imaging and SCA, though there were no clinically intervening events. Many patients with CAD also had single-vessel disease. The acquisition methods of L-mode for static vs. H-mode for dynamic acquisition and timing of 15 vs 20 minutes, respectively, could have impacted the count statistics and ultimately image analysis between clinical and dynamic SPECT methods, although there were no dramatic differences in sensitivity and specificity in these methods.

NEW KNOWLEDGE GAINED

A quantitative approach such as measuring CFR using dynamic SPECT imaging is a better mode of diagnosing CAD than visual assessment of stress and rest images from static SPECT images. This may have significant implications in the future development of deep learning methods for the diagnosis of cardiovascular disease.

CONCLUSIONS

This preliminary feasibility study employed a unique imaging protocol where both conventional and dynamic SPECT MPI studies were acquired with no additional radiation dose and no additional time in the clinic than a conventional cardiac SPECT study. Although the study was performed with a small number of patients, it supports the relative accuracy of dynamic SPECT in terms of quantification compared with conventional MPI. Finally, this study clearly demonstrated the value of CFR for identifying CAD, with high sensitivity and specificity, available only with the data generated from the dynamic SPECT method.

Acknowledgements

The authors would like to thank nuclear medicine technologists at the UCSF Imaging Center at China Basin for conducting patient scans. The study was supported in part by the National Institutes of Health under grant R01 HL050663.

Disclosure

The authors have no conflict of interest.

References

1. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. J Nucl Cardiol. 2004;11:171-85.
2. Sciagra R, Leoncini M. Gated single-photon emission computed tomography. The present-day ''one-stop-shop'' for cardiac imaging. Q J Nucl Med Mol Imaging. 2005;49:19-29.
3. Beller GA, Bergmann SR. Myocardial perfusion imaging agents: SPECT and PET. J Nucl Cardiol. 2004;11:71-86.
4. Huang JY, Huang CK, Yen RF, Wu HY, Tu YK, Cheng MF, et al. Diagnostic performance of attenuation-corrected myocardial perfusion imaging for coronary artery disease: A systematic review and meta-analysis. J Nucl Med. 2016;57:1893-8.
5. Shrestha U, Sciammarella M, Alhassen F, Yeghiazarians Y, Ellin J, Verdin E, et al. Measurement of absolute myocardial blood flow in humans using dynamic cardiac SPECT and ^{99m}Tc-tetrofosmin: Method and validation. J Nucl Cardiol. 2017;24:268-77.
6. Jin M, Yang Y, King MA. Reconstruction of dynamic gated cardiac SPECT. Med Phys. 2006;33:4384-94.
7. Iida H, Eberl S. Quantitative assessment of regional myocardial blood flow with Thallium-201 and SPECT. J Nucl Cardiol. 1998;5:313-31.
8. Alhassen F, Nguyen N, Bains S, Gould RG, Seo Y, Bacharach SL, et al. Myocardial blood flow measurement with a conventional dual-head SPECT/CT with spatiotemporal iterative reconstructions—a clinical feasibility study. Am J Nucl Med Mol Imaging. 2013;4:53-9.
9. Chen LC, Lin CY, Chen IJ, Ku CT, Chen YK, Hsu B. SPECT myocardial blood flow quantitation concludes equivocal myocardial perfusion SPECT studies to increase diagnostic benefits. Clin Nucl Med. 2016;41:e60–2.
10. Hsu B, Hu LH, Yang BH, Chen LC, Chen YK, Ting CH, et al. SPECT myocardial blood flow quantitation toward clinical use: A comparative study with ^{13}N-ammonia PET myocardial blood flow quantitation. Eur J Nucl Med Mol Imaging. 2017;44:117-28.
11. Nkoulou R, Fuchs TA, Pazhenkottil AP, Kuest SM, Ghadri JR, Stehli J, et al. Absolute myocardial blood flow and flow reserve assessed by gated SPECT with cadmium-zinc-telluride detectors using ^{99m}Tc-tetrofosmin: Head-to-head comparison with ^{13}N-ammonia PET. J Nucl Med. 2016;57:1887-92.
12. Gullberg GT, Reutter BW, Sitek A, Maltz JS, Budinger TF. Dynamic single photon emission computed tomography—basic principles and cardiac applications. Phys Med Biol. 2010;55:R111-91.
13. Ben-Haim S, Murthy VL, Breault C, Allie R, Sitek A, Roth N, et al. Quantification of myocardial perfusion reserve using

dynamic SPECT imaging in humans: A feasibility study. J Nucl Med. 2013;54:873-9.
14. Ziadi MC, Dekemp RA, Williams K, Guo A, Renaud JM, Chow BJ, et al. Does quantification of myocardial flow reserve using rubidium-82 positron emission tomography facilitate detection of multivessel coronary artery disease? J Nucl Cardiol. 2012;19:670-80.
15. Beanlands RS, Ziadi MC, Williams K. Quantification of myocardial flow reserve using positron emission imaging the journey to clinical use. J Am Coll Cardiol. 2009;54:157-9.
16. Murthy VL, Naya M, Foster CR, Hainer J, Gaber M, Di Carli G, et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. Circulation. 2011;124:2215-24.
17. Herzog BA, Husmann L, Valenta I, Gaemperli O, Siegrist PT, Tay FM, et al. Long-term prognostic value of ^{13}N-ammonia myocardial perfusion positron emission tomography added value of coronary flow reserve. J Am Coll Cardiol. 2009;54:150-6.
18. Slomka PJ, Berman DS, Germano G. Absolute myocardial blood flow quantification with SPECT/CT: Is it possible? J Nucl Cardiol. 2014;21:1092-5.
19. Slomka P, Berman DS, Germano G. Myocardial blood flow from SPECT. J Nucl Cardiol. 2016;24:278-81.
20. Wells RG, Timmins R, Klein R, Lockwood J, Marvin B, deKemp RA, et al. Dynamic SPECT measurement of absolute myocardial blood flow in a porcine model. J Nucl Med. 2014;55:1685-91.
21. Shepp LA, Vardi Y. Maximum likelihood reconstruction for emission tomography. IEEE Trans Med Imaging. 1982;1:113-22.
22. Shrestha UM, Seo Y, Botvinick EH, Gullberg GT. Image reconstruction in higher dimensions: Myocardial perfusion imaging of tracer dynamics with cardiac motion due to deformation and respiration. Phys Med Biol. 2015;60:8275-301.
23. Winant CD, Aparici CM, Zelnik YR, Reutter BW, Sitek A, Bacharach SL, et al. Investigation of dynamic SPECT measurements of the arterial input function in human subjects using simulation, phantom and human studies. Phys Med Biol. 2012;57:375-93.
24. Hudson HM, Larkin RS. Accelerated image reconstruction using ordered subsets of projection data. IEEE Trans Med Imaging. 1994;13:601-9.
25. Legrand V, Hodgson JM, Bates ER, Aueron FM, Mancini GB, Smith JS, et al. Abnormal coronary flow reserve and abnormal radionuclide exercise test results in patients with normal coronary angiograms. J Am Coll Cardiol. 1985;6:1245-53.
26. Gould KL, Johnson NP, Bateman TM, Beanlands RS, Bengel FM, Bober R, et al. Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. J Am Coll Cardiol. 2013;62:1639-53.
27. Yoshinaga K, Manabe O, Tamaki N. Absolute quantification of myocardial blood flow. J Nucl Cardiol. 2016;48:1783.
28. Schelbert HR, Phelps ME, Hoffman E, Huang SC, Kuhl DE. Regional myocardial blood flow, metabolism and function assessed noninvasively with positron emission tomography. Am J Cardiol. 1980;46:1269-77.
29. Schindler TH, Facta AD, Prior JO, Campisi R, Inubushi M, Kreissl MC, et al. Pet-measured heterogeneity in longitudinal myocardial blood flow in response to sympathetic and pharmacologic stress as a non-invasive probe of epicardial vasomotor dysfunction. Eur J Nucl Med Mol Imaging. 2006;33:1140-9.
30. Garcia EV. Are SPECT measurements of myocardial blood flow and flow reserve ready for clinical use? Eur J Nucl Med Mol Imaging. 2014;41:2291-3.
31. Petretta M, Storto G, Pellegrino T, Bonaduce D, Cuocolo A. Quantitative assessment of myocardial blood flow with SPECT. Prog Cardiovasc Dis. 2015;57:607-14.
32. Timmins R, Klein R, Petryk J, Marvin B, Wei L, deKemp RA, et al. Reduced dose measurement of absolute myocardial blood flow using dynamic SPECT imaging in a porcine model. Med Phys. 2015;42:5075-83.
33. Nose N, Fukushima K, Lapa C, Werner RA, Javadi MS, Taki J, et al. Assessment of coronary flow reserve using a combination of planar first-pass angiography and myocardial SPECT: Comparison with myocardial ^{15}O-water PET. Int J Cardiol. 2016;222:209-12.
34. Wang L, Wu D, Yang Y, Chen IJ, Lin CY, Hsu B, et al. Avoiding full corrections in dynamic SPECT images impacts the performance of SPECT myocardial blood flow quantitation. J Nucl Cardiol. 2016. doi:10.1007/s12350-016-0513-4.
35. Joutsiniemi E, Saraste A, Pietila M, Maki M, Kajander S, Ukkonen H, et al. Absolute flow or myocardial flow reserve for the detection of significant coronary artery disease? Eur Heart J Cardiovas Imaging. 2014;15:659-65.
36. Parker MW, Iskandar A, Limone B, Perugini A, Kim H, Jones C, et al. Diagnostic accuracy of cardiac positron emission tomography versus single photon emission computed tomography for coronary artery disease: A bivariate meta-analysis. Circ Cardiovasc Imaging. 2012;5:700-7.
37. Chareonthaitawee P, Kaufmann PA, Rimoldi O, Camici PG. Heterogeneity of resting and hyperemic myocardial blood flow in healthy humans. Cardiovasc Res. 2001;50:151-61.
38. Beller GA, Zaret BL. Contributions of nuclear cardiology to diagnosis and prognosis of patients with coronary artery disease. Circulation. 2000;101:1465-78.