Gated SPECT myocardial perfusion imaging with cadmium-zinc-telluride detectors allows real-time assessment of dobutamine-stress-induced wall motion abnormalities

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Background. **Left ventricular (LV) ejection fraction (EF) during high dobutamine stress (HD) by real-time gated-SPECT myocardial perfusion imaging (MPI) on a cadmium-zinc-telluride (CZT) gamma camera was validated versus cardiac magnetic resonance imaging (CMR).**

Methods and results. **After injecting 99mTc-tetrofosmin (320 MBq) in 50 patients (mean age 64 +/− 11 years), EF at rest and post-stress as well as relevant changes in EF at HD (ΔEF ≥ 5%) were assessed. CZT and CMR rest EF values yielded an excellent correlation and agreement ($r = 0.96$; $P < 0.001$; Bland–Altman limits of agreement (BA): + 0 to 14.8%). HD EF acquisition was feasible using CZT and correlated better to HD CMR EF than did post-stress CZT EF ($r = 0.85$ vs 0.76, respectively, all $P < 0.001$). Agreement in ΔEF detection between HD CMR and immediate post-stress CZT (reflecting standard acquisition using conventional SPECT camera unable to scan during stress) was 45%, while this increased to 85% with real-time HD CZT scan.**

Conclusion. **Real-time ultrafast dobutamine gated-SPECT MPI with a CZT device is feasible and provides accurate measurements of HD LV performance. (J Nucl Cardiol 2019;26:1734–42.)**

Key Words: Cadmium-zinc-telluride detectors gamma camera • Dobutamine-stress • Wall motion abnormalities

Abbreviations			
CMR	Cardiac magnetic resonance imaging	LVWT	Left ventricular wall thickening
CZT	Cadmium-zinc-telluride detectors	MPI	Myocardial perfusion imaging
SPECT	single photon emission computed tomography	TID	Transient ischemic dilation
LVWM	Left ventricular wall motion		

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INTRODUCTION

Myocardial perfusion imaging (MPI) using single photon emission computerized tomography (SPECT) is one of the best established imaging modalities for the non-invasive detection of patients with coronary artery disease (CAD). This is partly due to the fact that perfusion abnormalities, which are the target of SPECT MPI, occur very early in the ischemic cascade.[1] Implementation of ECG-gated acquisition has improved the accuracy of SPECT as it allows to distinguish between true fixed defects and attenuation artifacts[2] and it confers an added prognostic value over MPI alone.[3] Dynamic changes in global and regional LV contractility under stress conditions are a strong predictor of adverse events in a wide range of cardiovascular conditions including CAD,[4-6] dilated cardiomyopathy,[6] and valvular dysfunction.[7]

The current SPECT gamma camera generation requires an acquisition time for MPI and gated-SPECT of 15 minutes or longer. This precludes an assessment of LV function and diameter during maximal stress. Thus, the widely used transient ischemic dilation (TID) is based on values assessed after stress, and could therefore be subject to changes due to early recovery during the relatively long scan period. The latest generation of SPECT cameras with cadmium-zinc-telluride (CZT) detector technology offers ultrafast MPI assessment at 3 minutes acquisition time[8,9] and may therefore be potentially used for sequential real-time EF acquisition by gated-SPECT at each step of a standard dobutamine stress protocol. We thus aimed at evaluating the feasibility of EF measurements and its accuracy to detect clinically relevant changes in EF (ΔEF) during standard dobutamine stress protocol assessed by real-time high-speed gated-SPECT using cardiac magnetic resonance imaging (CMR) with dobutamine stress as standard of reference.

MATERIAL AND METHODS

Patient Population

Fifty consecutive patients referred for SPECT MPI were enrolled for the feasibility study (including reproducibility and repeatability for the rest scan). Exclusion criteria were any contraindication to dobutamine including recent unstable angina, uncontrolled hypertension, aortic aneurysmal disease, or severe aortic stenosis. An additional rest/dobutamine-CMR was performed in a subgroup of 20 within 2 weeks during which no change in clinical condition including medication or revascularization occurred for validation of the precision. The study was approved by the local ethics committee and all study participants provided written informed consent.

Stress Protocol

After a rest ECG and obtaining an intravenous line, dobutamine was administered intravenously by an infusion pump, starting at a low dose of 10 ug/kg/min (LD) for 5 minutes and then increasing by 10 ug/kg/min every 3 minutes, to achieve 85% of age-predicted maximal heart rate (220-age), up to a maximum of 40 ug/kg/min. Atropine 0.5 to 1 mg iv was added whenever needed to achieve the target heart rate. Throughout the pharmacologic stress continuous 12-lead ECG and intermittent blood pressure monitoring were recorded. Dobutamine was stopped prior to reaching the target heart rate in case of severe hypertensive response (blood pressure $>$ 220/120 mm hg), systolic hypotension ($<$ 80 mm Hg), blood pressure drop $>$ 40 mm Hg compared to baseline, significant arrhythmia, horizontal or downsloping ST segment depression $>$ 0.20 mV at an interval of 80 ms from the J point compared to baseline, ST segments elevation $>$ 0.1 mV in patients without previous myocardial infarction.[10]

SPECT Data Acquisition and Reconstruction

All SPECT MPI's were performed on a hybrid CZT/CT device (DNM 570c, GE Healthcare, Milwaukee). The CZT part is a gamma-camera equipped with 19 non-rotating CZT solid state detector modules positioned around the chest.[11-13] This camera enables low-dose radiotracer MPI acquisition within 3 minutes and high-dose radiotracer acquisition within 2 minutes.[8] After a CT scan for attenuation correction,[14,15] 320 MBq of ^{99m}Tc-tetrofosmin were injected, and MPI as well as LV function were assessed at rest twice consecutively over 3 minutes each. Thereafter, dobutamine was started and LV function was assessed from gated-MPI (3 minutes acquisitions each) after reaching a steady-state during low-dose dobutamine (LD) (10 ug/kg/min) and at peak-stress during maximum dobutamine dose (HD). Immediately after finishing HD image acquisition, 960 MBq of ^{99m}Tc-tetrofosmin was injected while dobutamine was continued for 1 more minute and gated post-stress images were acquired 5 min later. Thus, this protocol allows assessing MPI at rest and at HD stress, but also allows LV functional data at rest, at LD and HD, as well as early post-stress. The latter reflects the traditional setting with a standard SPECT camera which does not allow real-time LV function assessment because acquisition time exceeds by far the short time of HD dobutamine tolerable by patients. The widely used TID is based on such post-stress data which may

substantially differ from the real value at stress. All SPECT images were acquired with ECG gating and in list-mode.[9,11] A schematic representation of the scanning protocol is displayed in Figure 1.

Reconstruction of gated-SPECT was performed using dedicated software (Myovation for Alcyone, GE Healthcare, Milwaukee) including CT-based attenuation correction as previously described[14] and validated for this CZT device[15]: list-mode files were used to generate 2 separate rest MPI gated scans (3 minutes each). All scans were rebinned into 8 frames encompassing the entire R-R interval with a 10% acceptance window for bad-beat rejection. Reconstructed files were analyzed using the commercially available QGS/QPS software package (Cedars Sinai, California, USA) yielding quantitative values for left ventricular (LV) end-diastolic (EDV) and end-systolic volumes (ESV), and ejection fraction (EF). Regional values of LV wall motion (LVWM) and thickening (LVWT) were generated for each coronary artery territory, i.e., left anterior descending (LAD), circumflex (CX), and right coronary artery (RCA) according to standardized myocardial segmentation models.[16] Cardiac output was calculated as the product of stroke volume (EDV minus ESV) times heart rate. The rest studies were assessed for repeatability by a single observer. Stress ECG and list mode heart rate display were reviewed for quality control.

CMR Acquisition and Reconstruction

All CMR studies were performed in expiration using a 1.5 Tesla system (Achieva, Philips Medical Systems, Best, the Netherlands) with prospective ECG-triggering. Scout images served to determine 4-chamber, 2-chamber, 3-chamber views, and 3 basal to apical short-axis views of the left ventricle. Volume measurements were obtained after multiphase gradient-echo (repetition time/echo time 30/10 ms, section thickness 10 mm, flip angle 40-50, matrix of 128 × 128 reconstructed in 256 × 256). Measurements during LD and HD were performed after injection of contrast media used for rest perfusion evaluation (0.1 mmol of gadolinium per kilogram of body weight, Gadovist 1.0; Bayer Schering Pharma, Berlin, Germany). LV volumes were calculated from the gradient-echo MR images using an analytical software package (QMass MR, version 7.2; Medis Medical Imaging systems, Leiden, the Netherlands). After endocardial delineation, EDV and ESV were identified as the frames with maximal and minimal cavity volume. Regional contractility was analyzed visually by two experienced readers at rest and during dobutamine infusion.

Statistical Analysis

Values were expressed as mean (SD) or median with interquartile range (IQR) where appropriate. Means were compared using a two-tailed paired-t test or Mann–Whitney U test, respectively. Correlation between measurements was assessed using Pearson's correlation and systematic biases were illustrated by Bland–Altman limits of agreement.[17] The variation between measurements was expressed by the coefficient of variation (COV = 100 * standard error of the mean/ mean of the

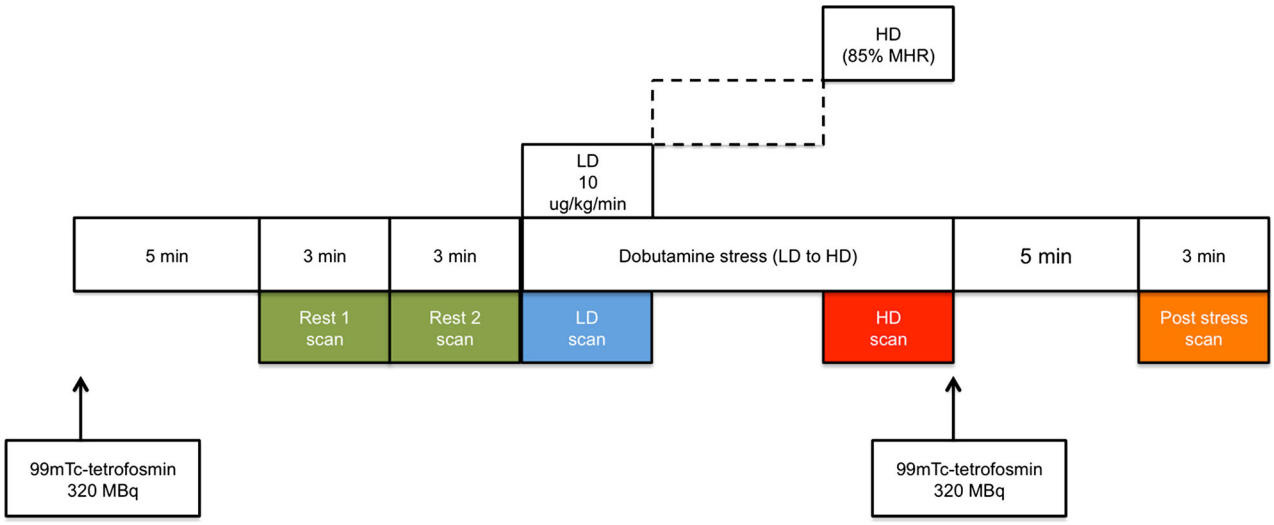

Figure 1. Scanning protocol for real-time acquisition of EF during SPECT MPI. *CTAC*, computed tomography attenuation correction scan; *MHR*, age-predicted maximal heart rate; *LD*, low-dose dobutamine; *HD*, peak-stress at high-dose dobutamine; *P dobu*, post-stress.

Table 1. Baseline characteristics of the study population

	All SPECT MPI	SPECT MPI with CMR
n	50	20
Male sex, *n* (%)	37 (74)	15 (75)
Age in years, mean (SD)	64 (11)	63 (10)
Body mass index in kg/m^2, mean (SD)	26.9 (4.9)	26.3 (4.3)
Known CAD, *n* (%)	15 (30)	5 (25)
Cardiovascular risk factors, *n* (%)		
Hypertension	38 (76)	12 (60)
Dyslipidemia	27 (54)	11 (55)
Diabetes	8 (16)	6 (30)
Smoking	16 (32)	8 (40)

MPI, myocardial perfusion imaging; *CAD*, coronary artery disease; *CMR*, cardiac magnetic resonance imaging

Table 2. Global and regional functional parameters during sequential gated-SPECT under dobutamine

n = 50, mean (SD)	Rest	LD	HD	Post-stress
EF	49 (15)	51 (16)	62 (18)*	56 (17)**
EDV	107 (59)	112 (63)	91 (52)*	102 (62)**
ESV	60 (63)	62 (50)	42 (49)*	53 (63)**
CO	3.06 (0.86)	3.65 (1.18)*	6.45 (1.83)*	4.22 (1.72)**
LVWM	6.1 (2.4)	6.3 (2.3)	7.8 (3.2)*	7.1 (2.9)**
LVWT	29 (14)	31 (15)	43 (21)*	33 (16)**

LD, low-dose dobutamine; *HD*, peak-stress at high-dose dobutamine; *EF*, left ventricular ejection fraction in %; *EDV*, end diastolic volume in mL; *ESV*, end systolic volume in mL; *CO*, cardiac output in L/min; *LVWM*, left ventricular wall motion in mm; *LVWT*, left ventricular wall thickening in per vessel territory in%
*Denotes significant changes ($P < 0.05$) compared to rest
**Denotes significant changes compared to HD

estimates). Agreement rates between trends of EF during SPECT and CMR were provided. A ΔEF change > 5% between rest and peak-stress was considered to denote clinically a significant change. Receiver operator characteristics (ROC) analysis was used to derive optimal cut-off points for LVWM and LVWT to discriminate coronary territories presenting with at least one dysfunctional segment on stress CMR. All P values < 0.05 were considered statistically significant.

RESULTS

Baseline characteristics of the study population are summarized in Table 1. All fifty patients completed the SPECT MPI successfully and without complication. No patient presented with atrial fibrillation or significant rhythm irregularity. The median examination time of the entire CZT MPI was 48 min (IQR: 42-58 minutes). Of all 50 patients, 9 (18%) did not reach their target maximal heart rate despite optimal pharmacologic stress doses. In 1 patient, dobutamine infusion was discontinued early due to chest pain associated with > 2 mm ST segment depression and blood pressure drop of 20 mm Hg. There were no significant differences between the subgroup of patients undergoing additional CMR and the entire population with regard to baseline characteristics.

Repeatability of Volume Assessment by Gated-SPECT

Table 2 shows mean volumes and functional parameters at rest and during dobutamine stimulation. Fifteen patients presented with a rest LVEF lower than 45% by gated SPECT. The correlation obtained by repeat rest evaluations was excellent for EF ($r = 0.99$; $P = 0.001$), EDV ($r = 0.97$; $P = 0.001$), ESV ($r = 0.99$; $P = 0.001$), LVWM ($r = 0.92$; $P = 0.001$), and LVWT ($r = 0.93$; $P = 0.001$). These values showed a COV of 4%, 12%, 13%, 16%, and 18%, respectively. Correlation and Bland–

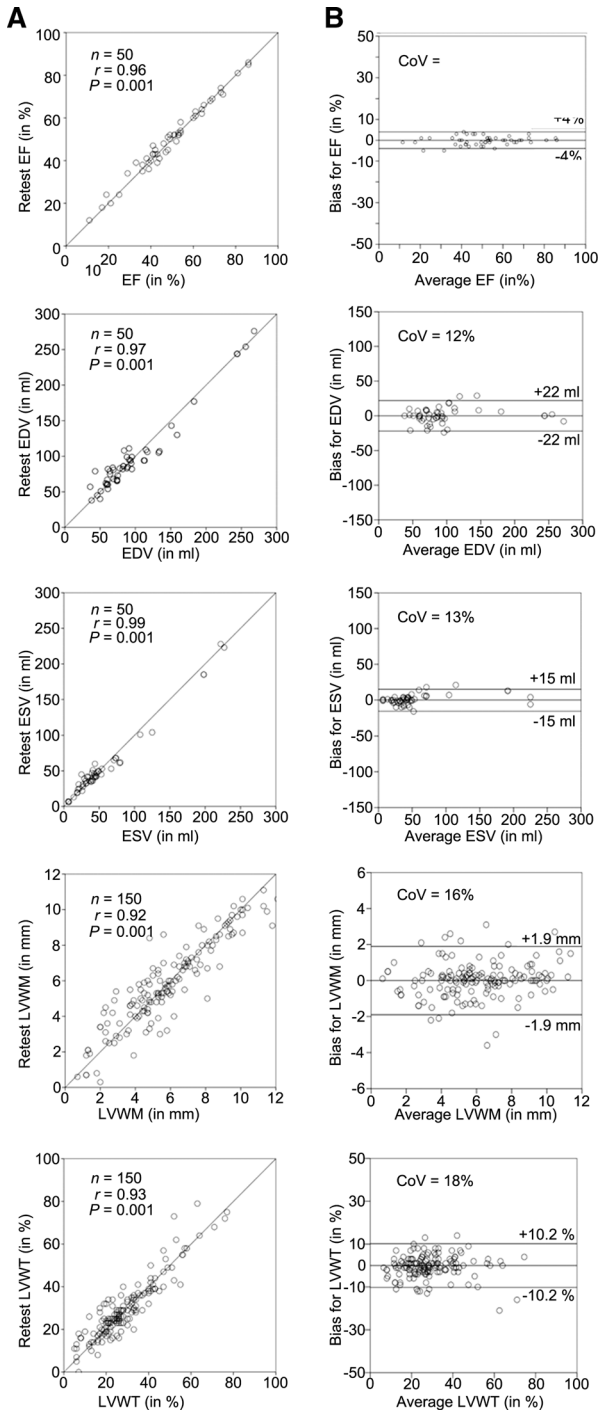

Figure 2. Correlation (**A**) and Bland–Altman bias (**B**) obtained during repeated evaluation of volumes and contractile parameters. *EF*, ejection fraction; *EDV*, end systolic volume; *ESV*, end systolic volume; *LVWM*, left ventricular wall motion; *LVWT*, left ventricular wall thickening; *CoV*, coefficient of variation.

Altman plots of volumes and contractile parameters during repeat rest examinations are displayed in Figure 2.

Correlation with CMR Volume Assessment

The parameters of LV function obtained at rest and peak-stress using gated-SPECT and CMR are provided in Table 3. An excellent correlation was found between CMR and gated-SPECT for rest EF ($r = 0.96$; $P = 0.001$; BA limits of agreement, + 0% to + 14.8%), EDV ($r = 0.91$; $P = 0.001$; + 0 to + 86 mL), and ESV ($r = 0.96$; $P = 0.001$; − 14 to + 34 mL) (Figure 3). At peak-stress and post-stress, these correlations for EF, EDV, and ESV were, respectively, of 0.85, 0.70, 0.77 and 0.76, 0.49, 0.69, respectively (all $P < 0.001$). At HD, gated-SPECT identified 14 of 16 patients with $\Delta EF \geq 5\%$, and 3 of 4 with stable or decreasing ΔEF by stress CMR resulting in an agreement rate of 85% (17/20 patients; kappa= 0.57; 95% CI: 0.14 to 1). Post-stress gated-SPECT allowed identifying 8 of 16 patients with increasing ΔEF, and 1 of 4 with stable or decreasing ΔEF by stress CMR with an agreement rate of 45% (9/20 patients; kappa = − 0.17; CI − 0.5 to 0.18).

Optimal Cut-Off Value for LVWM and LVWT

Visual analysis of regional contractility in coronary territories using CMR at rest (60 territories) and at HD (60 territories) revealed contractile dysfunction in 27/120 coronary territories LAD, CX, RCA territories affected on 6, 9, and 12 occasions. Table 4 summarizes the results from ROC analysis and optimal cut-off values of LVWM and LVWT to detect regional wall motion abnormalities on CMR. An illustrative case of the added value of real-time peak-stress over conventional post-stress gated-SPECT acquisition is presented in Figure 4.

SPECT Perfusion Findings

Perfusion studies revealed normal/abnormal findings in 38/12 patients and 133/17 coronary territories (7 on LAD, 6 on CX, and 4 on RCA territories, respectively). LVWM and LVWT abnormalities were associated with perfusion defects in 13 and 11 coronary territories during HD, and in 13 and 14 post-stress. Also, 24 and 22 additional coronary territories with normal perfusion findings showed abnormal LVWM and LVWT, respectively, during HD while 24 and 32 proved abnormal during post-stress study, respectively. However, a disagreement between HD and post-stress acquisitions concerning LVWM and LVWT abnormalities was observed in 22/150 (agreement rate: 85%) and 28/150 (agreement rate: 81%) coronary territories, respectively. In those patients with both CZT MPI and CMR, the CZT MPI revealed normal/abnormal findings in 13/7 patients. Only 1 patient with abnormal perfusion finding by CZT MPI did not denote increased ΔEF

Table 3. Parameters of left ventricular function at rest, peak-stress, and post-stress using gated-SPECT (CZT) and MRI

n = 20 Mean (SD)	Rest			HD			Post-stress	
	CMR	CZT	*r*	CMR	CZT	*r*	CZT	*R'*
EF	58 (13)	50 (14)	0.96*	67 (13)	64 (17)	0.85*	61 (17)	0.76*
EDV	141 (54)	95 (48)	0.91*	89 (21)	80 (41)	0.70*	88 (51)	0.49*
ESV	64 (51)	51 (46)	0.96*	23 (11)	37 (39)	0.77*	41 (49)	0.69*

CZT, myocardial perfusion imaging using ultrafast cadmium-zinc-telluride gamma camera; *CMR*, cardiac magnetic resonance imaging; *HD*, peak-stress at high-dose dobutamine; *EF*, left ventricular ejection fraction in %; *EDV*, end diastolic volume in mL; *ESV*, end systolic volume in mL; *CO*, cardiac output in L/min; *HR*, heart rate in beats/min; *r* = Pearson correlation value between CMR and CZT; *R'* = Pearson correlation value between CMR HD and CZT post-stress
* All *P* values < 0.001; n.a: not available

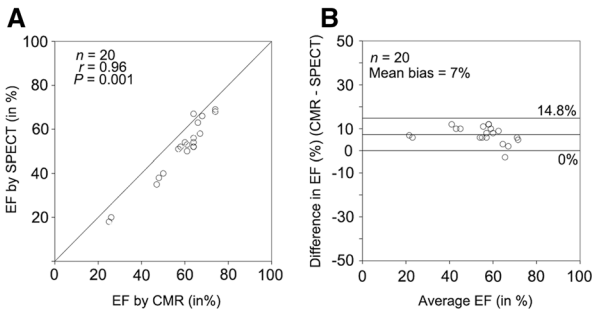

Figure 3. Correlation (**A**) and Bland–Altman graph (**B**) between ejection fractions (EF) obtained using SPECT and CMR.

change at stress by CMR. A perfect agreement between CMR and gated SPECT at HD was observed for trends in ΔEF, whereas disagreement was observed in one patient with increasing ΔEF by CMR and stable ΔEF by gated SPECT at post-stress.

DISCUSSION

The findings of the present study demonstrate that, using a novel CZT-equipped ultrafast SPECT camera, real-time peak-stress gated SPECT is feasible with short acquisition times of 3 min allowing accurate measurements of LV volumes and function during sustained maximal stress. So far, assessment of TID is based on the comparison of LV volumes at rest versus post-stress, as the current SPECT camera generation does not allow ultrafast scanning in order to evaluate volumes at the short peak-stress period. Nevertheless, TID has been shown to confer significant added diagnostic and prognosis value.[18,19] However, it seems reasonable to assume that TID calculated from volumes during peak-stress would be favorable as this may better reflect the ischemic reaction while the post-stress volumes may underestimate this due to recovery. This is supported by the fact that there was an excellent agreement between peak-stress LVEF from CZT compared to CMR, while

Table 4. Detection of abnormal LV wall motion (LVWM, in mm) and thickening (LVWT, in %) by gated-CZT SPECT validated versus CMR findings

		Sensitivity (%)	Spécificity (%)	Optimal cut-off	AUC	95% CI	*P* value
LVWM	LAD	96	84	4.8	0.87	0.68-0.97	0.003
	CX	66	89	7.9	0.82	0.68-0.96	0.003
	RCA	83	100	4.1	0.93	0.86-100	0.001
LVWT	LAD	86	84	32	0.83	0.73-0.94	0.01
	CX	64	100	27	0.91	0.81-100	0.001
	RCA	60	92	28	0.84	0.71-0.96	0.001

Sensitivity and specificity are given for each cut-off value as determined by the receiver operator characteristics area under the curve analysis
AUC, area under the curve; *LVWM*, left ventricular wall motion; *LVWT*, left ventricular wall thickening; *LAD*, left anterior descending artery territory; *CX*, circumflex artery territory; *RCA*, right coronary artery territory; *CZT*, myocardial perfusion imaging using ultrafast cadmium-zinc-telluride gamma camera; *CMR*, cardiac magnetic resonance imaging

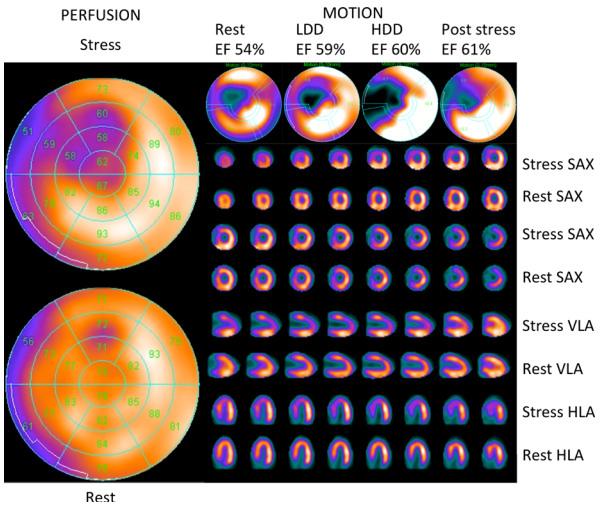

Figure 4. Illustrative case showing contractile dysfunction under increasing doses of dobutamine in a patient with proximal occlusion of the left anterior descending artery. The perfusion findings denote anterior perfusion defect in the same territory. *EF*, ejection fraction; *LD*, low-dose dobutamine; *HD*, high-dose dobutamine; *SAX*, short axis view; *VLA*, vertical long axis view; *HLA*, horizontal long axis view.

LVEF from post-stress SPECT—reflecting daily routine with standard SPECT equipment—showed a modest agreement. Despite short acquisition time of 3 min, the improved count sensitivity enabled by the new CZT camera allowed highly repeatable EF measurements with a variability of only 4%. High repeatability is a prerequisite for clinical follow-up of individual patients and comparison of repeat EF acquired during different hemodynamic conditions or after therapeutic interventions. It is also important in clinical studies to reduce the sample size in longitudinal studies. The present results compare well to the variability of 4% reported for EF from CMR,[20-22] and is superior to values from echocardiography where variability tends to be higher.[22-24]

One of the major strengths of perfusion SPECT is its established prognostic value based on semi-quantitative scoring which has substantially improved standardization and significantly reduced observed variability, not only for assessing perfusion but also for evaluating wall motion, global EF and segmental contractility. By contrast, other modalities such as CMR or echocardiography widely rely on an eye ball reading as standardized semi-automated analysis tools are limited.[25] Our results extend the reliability of functional LV measurements to the latest generation of CZT-equipped gamma camera. Furthermore, this type of scanner enables functional LV assessment during dobutamine stress allowing evaluation of regional stress-induced contractile dysfunction.[26,27] Using the respective cut-off from ROC LVWM and LVWT yielded a high accuracy to detect abnormal contractility with CMR as standard of reference in all coronary territories.

The proposed acquisition protocol using the CZT gamma camera offering the opportunity of fast gated acquisitions during subsequent stages of a dobutamine stress may confer and added diagnostic value in evaluation of multivessel CAD. In fact, MPI is limited to detection of relative perfusion defects, which may underestimate the true extent of myocardial ischemia in coronary territories adjacent to areas with more severe lesions.[23] Although extensive coronary calcification may unmask an underlying multivessel disease,[28,29] stress-induced wall motion abnormalities would provide direct proof of functionally relevant ischemia such as in stress echocardiography or stress CMR.[30-33]

We acknowledge the following limitations: First, although the examination time was similar between our standard protocol and the new proposed protocol (namely 30 minutes for the entire dobutamine stress and 30 minutes for image acquisition including positioning the patient, attenuation scan and MPI's acquisition), the new protocol represents increased scanner occupancy time since the CZT camera cannot be used for another acquisition during the full length of examination. However, this could be avoided by preselecting patients with high likelihood of extensive coronary calcifications or multivessel disease for this specific protocol. Such patients would also justify the selection of the stress agent dobutamine that is seldom used as compared to vasodilator stressing agents in patients unable to provide a significant physiologic stress test. Second, the CMR examination which served as standard of reference was not performed on the same day, although this may have helped minimizing biological variability of functional LV parameters. However, it is questionable whether the biologic response to dobutamine stress would have been identical in a one-day protocol, particularly in view of prolonged ventricular dysfunction observed after dobutamine stress in patients with CAD.[34] Third, TID as it is described in the literature reflects a combination of true dilation and diffuse subendocardial hypoperfusion at stress. Using standard gamma camera, this information was gathered during the post-stress period when the heart rate had returned to baseline and enabled comparison of EDV after similar filling time at stress and rest. Assessing the EDV at peak-stress to compute the TID introduces a reduced filling time owing to increased heart rate and that may limitate comparison between TID at peak-stress and post-stress. Fourth, the present article does not explore the diagnostic accuracy of dobutamine CZT as compared to dobutamine CMR in the detection of stress-induced regional contractile dysfunction. This might be assessed in further studies taking into consideration

limitations related to our low temporal resolution (8 bin gated) but also complex modifications of wall motion and thickening within the same territory depending on the extent of stress-induced perfusion defect and viability status. Furthermore, our proposed derivated LVWM and LVWT regional values have to be validated in different cohorts of patients before integration as diagnostic reference value. Finally, due to the pilot nature of your study, we did not include a large number of patients with obesity or other features associated with a reduced accuracy of SPECT neither did we discuss on the match between perfusion and contractility. Therefore, our data should be interpreted with caution with regard to extrapolation to other patient populations.

NEW KNOWLEDGE GAINED

Due to the fast acquisition with whole heart coverage, modern CZT cameras allow left ventricular volumes and wall motion assessment during peak-stress. The distinction of wall motion abnormalities observed at peak-stress versus post-stress may offer added information the interaction and time course of ischemia and its impact on contractility.

CONCLUSION

Real-time ultrafast dobutamine gated-SPECT MPI with a CZT device is feasible and provides accurate measurements of peak-stress LV performance.

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Disclosures

None declared.

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