Low-dose dobutamine stress gated blood pool SPECT assessment of left ventricular contractile reserve in ischemic cardiomyopathy: a feasibility study

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Abstract

Purpose: The purpose of present study was to assess the feasibility of GBPS with low-dose dobutamine (LDD) stress test, performed on a SPECT camera equipped with Cadmium-Zinc-Telluride (CZT) solid state detectors in evaluation of patients with ischemic heart failure (HF).

Methods. A total of 52 patients with ischemic cardiomyopathy (ICM) and a control group of 10 patients without obstructive coronary artery lesion underwent GBPS and transthoracic echocardiography (TTE) at rest and during LDD stress test (5, 10, 15 $\mu\text{g/kg/min}$). The duration of each GBPS step was 5 minutes. Stress-induced changes (Δ) in LV ejection fraction (LVEF), peak ejection rate, LV volumes and dyssynchrony (phase histogram standard deviation, phase histogram bandwidth and entropy) obtained with GBPS were estimated.

Results. All GBPS indices except end-diastolic volume showed significant dynamics during stress test in both groups. 17% of ICM patients, but none from control group, showed a decrease in EF during stress, accompanied by a significant increase in entropy. The inter-rater reproducibility was excellent for both rest and stress studies. There was a moderate correlation ($r=0.5$, $p=0.01$) between GBPS and TTE, with a mean difference value of -1.7 (95% confidence interval -9.8; 6.4; $p=0.06$) in ΔLVEF .

Conclusion. Low-dose dobutamine stress gated blood pool SPECT performed with high-efficiency CZT-SPECT cameras allow evaluation of stress-induced changes in LV contractility and dyssynchrony in patients with ischemic HF. The high sensitivity of the semiconductor detectors provides an opportunity to perform GBPS with lower acquisition time and a decrease in patient radiation exposure.

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Introduction

Equilibrium radionuclide angiography (ERNA) is a well-established imaging modality for the assessment of cardiac function due to its high accuracy and reproducibility [1]. However, data are lacking regarding the use of ERNA with inotropic pharmacological stress tests. Previously published articles have demonstrated the prognostic value of planar stress ERNA and have shown that it may be used as an alternative to exercise testing for risk stratification [2, 3, 4]. Saliman S. et al. have described stress gated blood pool SPECT (GBPS) in an experimental study on canine models [5]. In this paper, the study duration was of approximately 140 min, which is inappropriate for clinical practice. Introduction of gamma cameras with solid-state semiconductor cadmium zinc telluride (CZT) detectors allows to significantly shorten the imaging time [6, 7, 8], an important feature which could be implemented in GBPS.

The aim of present study was to evaluate the performance of low-dose dobutamine (LDD) gated blood pool SPECT using a CZT camera to assess LV contractile reserve in patients with ischemic cardiomyopathy (ICM). To the best of our knowledge, this is the first study specifically performing GBPS

using a CZT camera in patients with severely reduced left ventricular systolic function and ejection fraction (LVEF).

Materials And Methods

Patient and Study Population

Between 2018 and 2019, a total of 77 patients with ICM and a control group 10 patients without obstructive coronary artery disease were enrolled in the study.

Inclusion criteria for ICM patients were: reduced LV systolic function with an EF < 40% and an increase in LV volumes demonstrated by transthoracic echocardiography (TTE), history of myocardial infarction or revascularization (coronary artery bypass grafting or percutaneous coronary intervention), > 75% stenosis of left main or > 75% stenosis in the proximal left anterior descending artery, and/ or stenosis of > 75% of two or more epicardial vessels based on invasive coronary angiography results [9]. Inclusion criteria for the control group were the absence of obstructive coronary artery lesion, no history of myocardial infarction or revascularization. Exclusion criteria were patients who had contraindications to the LDD stress test – with acute coronary syndrome, severe aortic valve stenosis, hypertrophic cardiomyopathy, hemodynamic instability, inflammatory myocardial diseases, atrial fibrillation, severe hematological or neurological disorders and patients who could not sign a consent form. The study was approved by the Local Ethical Committee and conformed to the Declaration of Helsinki on Human Research. Written informed consent was obtained from each patient after explanation of the protocol, its aims, and potential risks. This research is part of SciCoRIC study (ClinicalTrials.gov identifier: NCT04508608).

Study Design

According to the research protocol, all patients underwent LDD TTE followed by LDD GBPS within 1–3 days of each other.

Patient Preparation

The preparation for both LDD TTE and LDD GBSP is similar and was performed according to guidelines [10]. Prior to the test, an intravenous cannula was inserted in the right cubital vein of each patient.

Stress Protocol

Dobutamine was infused into a cubital vein starting at a dose of 5 µg/kg/min to achieve a stable response and then increased to 10 and 15µg/kg/min [10]. Each stage lasted for 5 min. A syringe pump Braun Perfusor Compact S (Braun, PA) was used. The 12-lead electrocardiogram (ECG) was monitored continuously during the entire examination. Blood pressure was measured at baseline and repeated at each stage of the dobutamine infusion.

Transthoracic Echocardiography

TTE was performed in all patients using the ultrasound system Vivid E9 (GE Healthcare) with matrix multi-frequency transducer (1.5–4.6 MHz).

2D M-mode, Doppler echocardiography measurements and quantification were performed according to recommendations of the American Societies of Echocardiography [11]. All TTE images were recorded and further analyzed by experienced echocardiographers in at least three cardiac cycles using a dedicated software (GE-Vingmed, Horten, Norway). Echocardiography parameters were recorded initially at rest, at 4–5 minutes of infusion of each dose of dobutamine, and during the recovery period. Common 2D echocardiography parameters including LV contractility, end-diastolic volume (EDV), and end-systolic volume (ESV), as well as assessment of valvular disease and pulmonary artery pressure were obtained.

GBPS Data Acquisition and Processing

All patients underwent rest and LDD stress gated blood pool SPECT (Discovery NM/CT 570c; GE Healthcare, Haifa, Israel) following in vivo labeling of red blood cells (RBC) with a 99mTc-pertechnetate (Tc-99m) activity of approximately 9 MBq/kg [1]. Patients were imaged in the supine position with the left arm placed over the head.

The data were acquired with ECG gating (16 frames/cycle; acceptance window of $\pm 15\%$) for 5 minutes with a 20% energy window centered at 140 keV. No attenuation correction was used.

The entire examination consisted of three acquisition series. The first series was acquired at rest. The second and third series were acquired at 10 and 15 $\mu\text{g/kg/min}$ of dobutamine, respectively. The acquisition was simultaneous with the dobutamine infusion through the entire duration of the stress.

GBPS Data Analysis

Raw data were analyzed visually for motion and attenuation artefacts. Quality control was performed according to the EANM guidelines [1]. Count statistics were assessed in a region of interest of 100 mm^2 placed in the center of the LV. Images were reconstructed on a dedicated workstation (Xeleris 4.0110; GE Healthcare, Haifa, Israel) using maximum-penalized-likelihood iterative reconstruction (60 iterations; Green OSL Alpha 0.7; Green OSL Beta 0.3). The Myovation for Alcyone software (GE Healthcare, Haifa, Israel) was used for image reconstruction. The Butterworth post-processing filter (frequency 0.52; order 5) was applied to the reconstructed slices obtained in a 70×70 pixels matrix with 57 slices.

Reconstructed images were processed using the Quantitative Blood Pool SPECT 2009.0 (Cedars-Sinai Medical Center, Los Angeles, CA, USA) software. The count-based volumes method was used to calculate EDV and ESV, as well as LVEF [1]. Ventricular contours were adjusted manually when required. The following LV parameters were evaluated in further analysis: EDV (ml), ESV (ml), EF (%), peak ejection rate (PER, expressed as EDV/s), phase histogram standard deviation (PSD, expressed in degree), bandwidth (HBW, expressed in degree) and entropy (expressed in percent, %). Changes in GBPS measured LV parameters or in the difference (delta, Δ) between the rest and the different stress test stages were

calculated as [the value at stress – rest value]. In cases of stress induced decline in LVEF, only the highest value of EF was used for further analysis.

Dosimetry

The effective dose to the patient for 99m Tc-RBCs was calculated using ICRP Publication 120 equation: 7.0×10^{-3} mSv/MBq of injected 99m Tc [12]

Interrater reproducibility

To test the interrater reproducibility 15 patients included in the ICM group were analyzed by two experienced nuclear medicine physicians blinded to each other's results.

Statistical Analysis

Data were assessed for normal distribution using the Shapiro–Wilk test. Continuous variables were expressed as mean $\pm$ standard deviation or as median with interquartile range (IQR) (Q25 to Q75). The Mann–Whitney U test and Wilcoxon signed-rank test were performed for unpaired and paired data, respectively. Each statistical test was 2-sided, and a p-value of < 0.05 was considered statistically significant. The Spearman test was used to estimate the correlation coefficient between quantitative variables. The Bland-Altman plot was used to assess mean differences between GBPS and TTE measurements.

For interrater reproducibility, the intraclass correlation coefficient (ICC) was calculated. Values below 0.50 were rated as poor reproducibility, 0.50–0.75 – moderate, 0.75–0.90 – good, and > 0.90 – excellent reproducibility. Statistical analyses were performed using STATISTICA 10.0 (StatSoft Inc, Tulsa, OK, USA) and MedCalc 17.4 (MedCalc Software, Mariakerke, Belgium).

Results

Among 77 patients with ICM who underwent LDD GBPS, 7 had no LDD TTE data, 5 had technical issues during the GBPS acquisition and 13 had side effects during stress procedure which resulted in interrupting the test and acquisition (6 patients had chest pain, 3 had an excessive hypertensive response and 4 had heart rhythm disturbances). As a result, 52 patients with ICM represent the final study population. Among the control group none had side effects during stress test, and therefore all 10 patients were enrolled (Fig. 1). The clinical characteristics of patients are presented in Table 1.

Table 1
Patient characteristics

	ICM (n = 52)	Control (n = 10)
Age	59 ± 7.2	52 ± 12.1
Hypercholesterolemia, n (%)	34 (65%)	7 (70%)
Hypertension, n (%)	42 (80%)	7 (70%)
Diabetes mellitus (type 2), n (%)	11 (21%)	2 (20%)
NYHA Class, n (%):		
0	0	8 (80%)
I	0	2 (20%)
II	24 (46%)	-
III	28 (54%)	-
History of MI, n (%)	52 (100%)	-
LVEF (%)*, n (%)	30 (27; 35)	64 (60; 65)
LV EDV (ml)*, n (%)	213 (190; 239)	106 (93; 117)
LV ESV (ml)*, n (%)	142 (130; 167)	39 (36; 40)
The number of CA with stenosis > 75%, n (%):		
1	4 (8%)	-
2	11 (21%)	-
3	37 (71%)	-
ICM – ischemic cardiomyopathy; NYHA – functional class of heart failure according to the New York Heart Association; MI – myocardial infarction; LV – left ventricular; EF – ejection fraction; EDV – end-diastolic volume; ESV – end-systolic volume; CA – coronary arteries; * - data obtained from echocardiography.		

Dosimetry

The mean injected ^{99m}Tc - RBC dose was of $750 \pm 111\text{MBq}$ (range 500–980 MBq) resulting in a mean effective radiation dose of $5.28 \pm 0.79\text{ mSv}$ (range 3.51–6.89 mSv) per patient.

Quality Assessment

The mean count rate at rest was of 214,247.0 (IQR 116,875.0; 295,940.0). During the stress study the rate decreased significantly to 186,600.0 (IQR 92,547.0; 297,955.0) counts ($p = 0.003$), but remained high (minimum value – 54,122.0; lower quartile – 92,547.0).

GBPS Interrater Reproducibility

The inter-operator reproducibility was excellent for both rest and stress studies (Table 2).

Table 2
The inter-operator reproducibility

	Rest		15 µg/kg/min	
	ICC	CI	ICC	CI
LV EDV	0.9625	0.8882; 0.9874	0.9974	0.9871; 0.9982
LV ESV	0.9612	0.8845; 0.9870	0.9943	0.9831; 0.9981
LV EF	0.9888	0.9667; 0.9962	0.9822	0.9469; 0.9940
LV PER	0.9779	0.9203; 0.9910	0.9808	0.9428; 0.9936
LV PSD	0.9959	0.9877; 0.9986	0.9745	0.9241; 0.9914
LV HBW	0.9968	0.9905; 0.9989	0.9952	0.9858; 0.9984
LV entropy	0.9957	0.9871; 0.9985	0.9953	0.9860; 0.9984
LV – left vertical; EF – ejection fraction; EDV – end-diastolic volume; ESV – end-diastolic volume; PER – peak ejection rate; PSD – phase histogram standard deviation; HBW – histogram bandwidth; ICC – inter-operator reproducibility; CI – confidence interval.				

LDD GBPS Results

For each stress stage, stress-induced changes in LV volumes, EF, and PER, and dyssynchrony parameters are presented in Figs. 2 and 3.

In the ICM group, 10 µg/kg/min dobutamine led to significant changes in all GBPS parameters except for EDV in comparison to rest. A dose of 15 µg/kg/min led to significant changes in LVEF, PER, ESV and PSD, when compared to rest parameters. There were no significant changes in any of the GBPS parameters at 15 µg/kg/min in comparison with 10 µg/kg/min. Nine ICM patients (17%) showed a decrease in LVEF during stress test accompanied by a significant increase in entropy (Fig. 4). In the control group, the dobutamine infusion at doses of 10 µg/kg/min and 15µg/kg/min led to significant changes in EF, PER, ESV and dyssynchrony indices (HBW and entropy) in comparison with rest measurements. PSD showed significant changes only at a dose of 15 µg/kg/min. LVEF and ESV changed significantly at the dobutamine dose of 15 µg/kg/min as compared to 10 µg/kg/min.

Stress-induced changes in GBPS parameters in ICM and the control groups are presented in Figs. 5 and 6. Only Δ EF at both 10 and 15 μ g/kg/min dobutamine doses, as well as Δ PER and Δ HBW at 15 μ g/kg/min were significantly higher in the control group as compared to ICM patients.

Comparison of LDD Stress GBPS and TTE

There was a moderate correlation ($r = 0.5$, $p = 0.01$) between LDD GBPS and LDD ECHO at peak stress. The Bland-Altman plot showed that both methods were comparable ($p = 0.06$) with mean difference value of -1.7 (96% CI -9.8; 6.4; $p = 0.06$) in Δ LVEF (Fig. 7).

Discussion

To our knowledge, this is the first CZT SPECT study measuring GBPS with LDD stress test in patients with ICM. The main finding of our study is that LDD GBPS allows the assessment of the LV contractile reserve and dyssynchrony changes in patients with ICM and LV dysfunction.

All GBPS parameters showed excellent reproducibility both at rest and stress. LV entropy in the ICM group showed the most significant changes during the stress test. Stress induced decrease in EF was accompanied by a simultaneous increase in entropy (but not PSD and HBW). In normal individuals, represent in present study by the 10 control cases, exercise will lead to an increase in LVEF. In disease, the inability of the heart to decrease the ESV and thus to increase the stroke volume leading to a decrease of the LVEF during exercise is an indicator for the presence and severity of stress induced ischemia [13]. This can also be explained by a decrease in some gene expression in the failing heart (i.e. SERCA2a) [14] or by myocardial remodeling post myocardial infarction [15].

Previous studies have shown that dobutamine stress planar ERNA can be performed in patients with ICM [2, 4]. The planar acquisition technique resulted in an underestimation of the LVEF, particularly in patients with LV systolic dysfunction (LVEF < 35%) and also lacked assessment of the LV dyssynchrony [8, 16]. SPECT ERNA avoids overlapping activity in cardiac chambers. The complete removal of counts from the left atrium resulted in a 7–10% higher LVEF when using SPECT ERNA as compared to LVEF obtained from planar ERNA and thus increased the accuracy of LV function assessment [8, 17].

Performing GBPS on conventional SPECT gamma-cameras takes about 20–30 min (32 frames with 40–60 seconds) per each acquisition [1]. Salimian et al. have applied GBPS with increasing doses of dobutamine using a dual-head gamma camera on a canine model using a 143 min dobutamine infusion and a high administered dose of radiopharmaceutical ~ 1,223 MBq, [Salimian S 2017]. This approach is non-applicable in clinical practice. CZT gamma-cameras allow to reduce the GBPS acquisition time to 8 min [18], 5 min [7] or even 4min [6]. In present study, we applied a 5 min acquisition protocol in combination with the LDD stress test.

Previous studies have demonstrated an excellent reproducibility of the LVEF and volumes obtained with GBPS at rest [19, 20]. SPECT ERNA is a very good tool for the assessment of LV dyssynchrony. Our findings of the stress induced changes in dyssynchrony parameters are similar to those of Boogers et al

[21], who used a conventional camera and showed good interrater reproducibility for both PSD and HBW in patients with ICM and LVEF $\leq 35\%$, ICC of 0.88 and 0.93, respectively. The lower ICC values in comparison to our study may be explained by the presence of large perfusion defects (typical in ICM) resulting in incorrect delineation of the myocardium [22]. GBPS avoids this drawback, since it delineates the blood pool and not the myocardium, resulting in more accurate measurements of volumes and function [23]. Moreover, Jensen et al. [24] reported better reproducibility results for rest GBPS parameters (LVEF and volumes) obtained with a CZT device as compared with Anger cameras (both planar and SPECT). Our study demonstrates reproducible results for all parameters, including dyssynchrony both at rest and stress, using a CZT gamma camera.

GBPS is a widely used imaging technique for assessment of myocardial contractility. This approach has diagnostic and prognostic significance in patients with HF including those with arrhythmia (particularly in CRT candidates) [25], pulmonary embolism [26] and cardiotoxicity [17, 20, 27]. This method was validated on cardiac phantom [28] and showed good correlation with CMR [29] and TTE [25]. However, this approach is not widely used for assessment of CR because of the relatively long study duration and high radiation exposure [8]. The CZT technology allows reducing the radiopharmaceutical dose to perform GBPS by up to 40% when the five minute acquisition protocol is applied or even by up to 50% in case of a 10-minute acquisition [8]. In present study the mean ^{99m}Tc - RBC administered dose was of $740 \pm 111\text{MBq}$, which is 40% lower than the dose recommended for stress studies [1], while at the same time image quality is preserved.

Left ventricular cardiac reserve is an index of global inotropic function increasing during both physical exercise and pharmacological stress test (usually with dobutamine), of well-established prognostic value [4, 30]. In patients with HF this parameter is used to assess the likelihood for improvement of the LVEF following treatment, whether medical, surgery [31] or device implantation [4, 30]. CR has been also shown to correlate with the amount of viable myocardium post infarction [32].

The most accepted criterion of preserved CR is a 5% absolute increase in LVEF during stress or a relative increase of 20% from the baseline rest LVEF [30, 32]. In present study the absolute increase in LVEF was of 4.5% (IQR 0; 9) in the ICM group and 14% (IQR 10; 19) in the control group, on average. CR remained unchanged in more than half of the ICM patients.

Clinical value of stress-induced change in mechanical dyssynchrony.

Numerous studies have shown that a high LV mechanical dyssynchrony (MD) value at rest is an independent predictor of all-cause mortality in ICM [14, 33, 34]. Kano et al [14] observed a significant inverse correlation between LV entropy and expression of the SERCA2a mRNA level, which mediates the contraction of cardiomyocytes and the re-entry of Ca^{2+} from the cytoplasm into the sarcoplasmic

reticulum. Lower amounts of SERCA2a mRNA are usually noticed in the human failing heart and its reduction is associated with Ca^{2+} handling impairment and contractile disorders [35].

Exercise or dobutamine stress test can be used to unmask LV dyssynchrony, which can be absent at rest. Such an approach can help identify high-risk patients [36]. Some studies have reported that patients undergoing CRT stress-induced changes in MD show a better correlation to clinical outcome and long-term survival than MD values at rest [37]. Currently, data regarding changes in MD during stress remain controversial. While some studies, using TTE reported that dyssynchrony is not a dynamic state and does not appear during stress [38, 39], other authors claim different patterns of stress-induced MD changes [40, 41]. Such controversial results may be due to the high variability of TTE [5].

We observed a significant decrease in all dyssynchrony parameters, particularly entropy, during stress-test in both groups of patients and controls, similar to some of previously published results [5, 42, 43].

Interestingly we observed a significant increase in entropy but not PSD and HBW in patients with ICM (n = 9) who showed a drop in LVEF at the dobutamine dose of 15 $\mu\text{g}/\text{kg}/\text{min}$. None of the control group subjects showed such a response.. This finding may be due to the fact that ischemia [44, 45] can appear during the stress test as a result of increasing myocardial oxygen demand [13] and could represent an additional sign of the extent of disease, in line with TID index [46].

Limitations

While the relatively small number of enrolled patients is a limitation of present study it seems sufficient considering this to be a first time feasibility project. In addition, in present study we assessed LV contractile function based on the 5 minute data acquisition. While there may be some averaging of the contractile function during the acquisition time, its effect, particularly at 10 and 15 $\mu\text{g}/\text{kg}/\text{min}$ of dobutamine, can be considered as insignificant because of dobutamine saturation at the dose of 5 $\mu\text{g}/\text{kg}/\text{min}$.

Conclusion

Low-dose dobutamine stress gated blood pool SPECT performed with high-efficiency CZT-SPECT cameras can identify stress-induced changes of LV contractility and dyssynchrony in patients with ischemic HF. Due to the high sensitivity of new semiconductor detectors there is an opportunity to perform GBPS with shorter acquisition time and lower radiation exposure to the patients. Further large scale clinical studies are needed to evaluate the potential clinical significance of this approach in patients with severe HF.

Declarations

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Ethics approval: All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Written and oral informed consent was provided by the patient involved in this study

Data availability: Not applicable.

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Figures

Figure 1

Study flow chart. ICM – ischemic cardiomyopathy; LDD – low-dose dobutamine.

Figure 2

Difference in LVEF (A), EDV (B), ESV (D) and PER (C) changes in the ICM and control groups. Blue line – ICM group; Green line – control group; LV – left ventricle; EF – ejection fraction; EDV – end-diastolic volume; ESV – end-diastolic volume; PER – peak ejection rate; ml – milliliter; s – seconds;

Figure 3

Dyssynchrony parameters changes in the ICM and control groups. A – phase histogram standard deviation (PSD); B – Entropy; C – histogram bandwidth (HBW). Blue line – ICM group; Green line – control group; LV – left ventricle.

Figure 4

Dynamics of LV entropy during stress test (A). Green line – group without decrease of LVEF; orange line – group with decrease of LVEF; green brackets – significance in group without decrease of LVEF; orange brackets – significance in group with decrease of LVEF. Delta of LV entropy between rest and 15 mcg/kg/min dobutamine study (B). Green bar - group without decrease of LVEF (no dEF); orange bar – group with decrease of LVEF (dEF).

Figure 5

Delta in LVEF (A), EDV (B), ESV (D) and PER (C) changes in ICM and control groups. Orange bar – ICM group; Green bar – control group. Δ – mean values of stress-induced changes between rest and stress acquisition; LV – left ventricle; EF – ejection fraction; EDV – end-diastolic volume; ESV – end-diastolic volume; PER – peak ejection rate; ml – milliliter; s – seconds

Figure 6

Delta of dyssynchrony parameters changes in ICM and control groups. Orange bar – ICM group, Green bar – control group; A – phase histogram standard deviation (PSD); B – Entropy; C – histogram bandwidth (HBW). Blue line – ICM group; Green line – control group; LV – left ventricle.

Figure 7

Comparison of ΔLVEF measured by LDD GBPS and LDD TTE: scatter plot (A) and Bland-Altman plot (B).