ORIGINAL ARTICLE

Prognostic significance of post-stress reduction in left ventricular ejection fraction with adenosine stress in Jordanian patients with normal myocardial perfusion

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Background. The significance of post-stress reduction in left ventricular ejection fraction (LVEF) in patients with normal perfusion on adenosine stress/rest imaging remains controversial.

Methods. Consecutive patients who underwent 2-day adenosine gated stress/rest ^{99m}Tc-sestamibi imaging and had normal perfusion were analyzed. LVEF was quantified at rest and 1 hour post-adenosine. Patients were followed up for hard (cardiac death or nonfatal MI) and soft (coronary revascularization or congestive heart failure) cardiac events for 24.1 ± 11.0 months.

Results. Of 560 patients included in the study, 135 (24.1%) had a post-stress reduction in LVEF of $\geq 5\%$. Rest LVEF ($P < 0.001$), known history of CAD ($P = 0.01$) and transient ischemic dilatation ratio ($P = 0.02$) were independent predictors of LVEF reduction. Event-free survivals were similar in patients with and without $\geq 5\%$ LVEF reduction ($P = 0.8$). The unadjusted hazard ratio (95% CI) for cardiac events for $\geq 5\%$ LVEF reduction was 1.09 (0.55-2.15), $P = 0.81$, while the hazard ratio adjusted for known history of CAD, smoking, post-stress LVEF and peak heart rate was 0.87 (0.44-1.75), $P = 0.71$.

Conclusions. Significant post-adenosine reduction in LVEF occurs in about one-fourth of patients with normal perfusion but does not confer adverse prognosis compared with patients without such reduction. (J Nucl Cardiol 2020;27:1596–606.)

Key Words: Gated SPECT · vasodilators · MPI · diagnostic and prognostic application

Abbreviations	
EF	Ejection fraction
LV	Left ventricular
MBq	Megabecquerel
mCi	Millicurie
SPECT	Single photon emission computerized tomography
SSS	Summed stress score
SRS	Summed rest score
SDS	Summed difference score
Tc-99m	Technetium-99m
MI	Myocardial infarction

INTRODUCTION

The presence of post-stress reduction in left ventricular ejection fraction (LVEF) by gated single-photon emission computed tomography (SPECT) has been described as a marker of underlying severe/extensive coronary artery disease (CAD) and adverse cardiac events.[1-9] Although the significance of post-stress reduction in LVEF is more established with exercise stress,[10-12] it has been also reported with vasodilator stress.[5,10-13] Vasodilator stress with agents, such as adenosine, differs from exercise stress in that it does not cause demand ischemia but it can induce ischemia in the presence of severe coronary artery stenos due to coronary steal syndrome.[14,15]

Two principle mechanisms have been proposed for the stress-induced reduction in LVEF following both exercise and vasodilator stress.[5,8,10,16,17] The first mechanism is a ''true'' post-stress myocardial stunning of areas with stress-induced ischemia, which can last 1 hour or longer following the end of stress.[18-22] The second mechanism pertains to possible underestimation of LVEF due to inaccurate tracking of endocardial surface in areas with severely decreased stress perfusion.[5,16,23] Common to both proposed mechanisms is the need for stress-induced perfusion abnormalities (defects), typically of severe degree as these abnormalities are necessary for both the development of true myocardial stunning and grossly inaccurate tracking of endocardial surface on gated stress images leading to underestimation of post-stress LVEF. Interestingly, however, stress-induced reduction in LVEF associated with severe/extensive CAD and/or adverse cardiac events has also been described in patients with normal stress perfusion.[8,17] The explanation of this finding is challenging although ''balanced ischemia'' has been proposed as a possible mechanism.[8,17] Yet, the frequency of stress-induced reduction in LVEF with normal stress perfusion has not been fully explored in studies involving large number of patients, including those undergoing vasodilator stress, such as adenosine. Moreover, in the absence of stress-induced ischemia, the significance of post-stress reduction in LVEF remains controversial. The aim of this study is to evaluate the frequency and prognostic value of post-adenosine stress reduction in LVEF in a large cohort of patients with normal perfusion on their scan.

METHODS

This retrospective study was approved by the Institutional Review Board (IRB) of Jordan University Hospital. The study cohort included all patients with known or suspected coronary artery disease who underwent a clinically indicated two-day adenosine-stress/rest gated SPECT study using ^{99m}Tc-sestamibi between January 1, 2015, and October 31, 2017, and had normal perfusion on their scan. The 2-day adenosine-stress/rest gated SPECT ^{99m}Tc-sestamibi was the standard myocardial perfusion imaging approach used at our institution during the study period because we intended to investigate the prevalence and prognostic significance of post-adenosine reduction in LVEF, and the 2-day protocol was deemed more suitable for this purpose since any stress-induced myocardial stunning would have completely recovered when patients are imaged at rest on a different day.[22]

Gated-SPECT Acquisition and Interpretation

Gated adenosine stress SPECT images were obtained 1 hour after injection of 15 mCi (555 MBq) of ^{99m}Tc-sestamibi (20 mCi [740 MBq] in obese patients) given 3 minutes into a 6-minute infusion of adenosine at a concentration of 140 μg/kg/min. Gated rest SPECT images were performed within one week thereafter, also 1 hour after injection of 15 mCi(555 MBq) of ^{99m}Tc-sestamibi (20 mCi [740 MBq in obese patients) with no intervening cardiac event or intervention between the stress and rest scans.

SPECT images were acquired using a dual-head gamma camera (E.CAM; Siemens Medical Solutions, Malvern, Pennsylvania, USA) equipped with a high-resolution parallel hole collimator with the peak energy set at 140 keV with a 20% window width, 180° rotation arc, 32 projections, 25 s/projection, 16 frames/heart cycle and 64 × 64 matrix. Processing was performed using filtered backprojection to transaxial tomographic images, and these were reoriented to the short, vertical and horizontal long axes. No attenuation correction was performed. We used beat-rejection software to acquire data with a stable R-R interval. A tolerance window of 20% was strictly enforced in all patients included in this study, and all beats outside this window were rejected. Patients with atrial fibrillation and PVCs, who made up about 5% of our patients, were only gated after applying this beat-rejection software.

Both the rest and post-stress scans were visually and semi-quantitatively assessed by two board-certified physicians

with > 10 years experience in nuclear cardiology using the quantitative automated software programs QPS and QGS (Cedar Sinai Medical Center, Los Angeles, CA) for the perfusion and functional parameters, respectively.[24] Both readers were blinded to patients' outcome.

Myocardial uptake in a 20-segment model was scored based on a 5-point scale ranging from 0 (normal uptake) to 4 (no detectable tracer uptake) with computation of the summed stress score (SSS) and summed rest score (SRS) for each patient by adding the scores of the 20 segments in the stress and rest images, respectively. The summed difference score (SDS) was computed as SSS-SRS. Scans with a SSS of ≤ 3 were considered negative (normal perfusion). Only patients with normal perfusion are included in the present study. QGS was used to measure the global LVEF, regional wall motion and thickness, LV end-systolic volume (LVESV) and LV end-diastolic volume (LVEDV) at rest and post-stress, while QPS was used to calculate the transient ischemic dilatation (TID) ratio.

The interobserver variability for the LVEF measure at our institution was determined based on ten patients whose rest and post-stress LVEF's were computed independently by two-board certified physicians using the QGS program. The reproducibility of the rest LVEF was found to be within 2.8%, which represented ± 2 SD of the mean difference between the two rest LVEF measurements performed by the two physicians while the reproducibility of post-stress LVEF was within 4.4% representing ± 2 SD of the mean difference between the two post-stress LVEF measurements.

The intraobserver variability for the LVEF measure was determined based on as set of another ten patients whose rest and post-stress LVEF's were computed twice by the same board-certified physician using the QGS program. In this case, the reproducibility of the rest and post-stress LVEF's was identical, within 2.6% representing ± 2 SD of the mean difference between the two rest LVEF measurements or the two post-stress LVEF measurements performed by the same physician.

Patient Outcome

Patients were followed up for both hard (cardiac death or nonfatal MI) and soft (coronary revascularization and congestive heart failure requiring hospitalization) cardiac events by review of hospital records and by telephone contact with the patient, relatives or referring physician. The mean follow-up period was 24.1 ± 11.0 months. Cardiac death was defined as that due to MI or sudden cardiac death ascertained as such by trained board-certified emergency room physicians or cardiologists.[25] Nonfatal MI was defined based on the third universal definition, the hallmark of which is the detection of a rise and/or fall of cardiac biomarker values, with at least one of the values being elevated (i.e., > 99th percentile upper reference limit, URL). High sensitivity troponin I is used in our laboratory in addition to one of the following conditions: symptoms suggestive of myocardial infarction, ECG changes, evidence of myocardial damage or identification of coronary thrombus. Coronary revascularization is defined as either

percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Congestive heart failure hospitalization is defined as hospitalization due to pulmonary edema diagnosed by clinical criteria, laboratory data and echocardiography.

Statistical Analysis

Categorical variables, reported as frequencies and as percentages, were compared using Pearson's χ^2 test or Fisher Exact test, as appropriate. Mann-Whitney U test was used to compare continuous variables. These were reported using means ± the standard deviations.

We examined the frequency, prognostic significance and predictors of LVEF reduction thresholds of $\geq 5\%$ and $\geq 10\%$, as previously reported in the literature.[7-9,23] Cardiac event-free survivals for reduction in LVEF $\geq 5\%$ and $< 5\%$ were compared using Kaplan-Meier plots and log rank test. The same approach was used to compare cardiac event-free survivals for reduction in LVEF $\geq 10\%$ and $< 10\%$. Hazard ratios for reductions in LVEF $\geq 5\%$ and $\geq 10\%$ were obtained through the Cox proportional hazard model.

Univariate analysis was first carried out to identify which variables among all possible variables known by published literature to potentially affect a certain outcome, such as LVEF reduction or cardiac events were significant predictors in our patient population. The variables included were age, sex, family history of CAD, known history of CAD, diabetes, hypertension, dyslipidemia, rest LVEF, post-stress LVEF, delta LVEF, TID ratio, rest and post-stress LVEDVs, rest and post-stress LVESVs and heart rate response (HRR), defined as maximum percent change in baseline heart rate post-adenosine.[26]

Multivariate analyses for possible independent predictor variables of cardiac events and LVEF reductions of $\geq 5\%$ and $\geq 10\%$ were carried out using the logistic regression model. Only significant variables ($P \leq 0.05$) by univariate analysis were entered into the multivariate analysis. Statistical significance was determined at two-sided P value ≤ 0.05. Analyses were performed in R version 3.5.0 and relevant package.[27]

RESULTS

The database query for the time period between January 1, 2015, and October 31, 2017, yielded 587 patients who underwent 2-day adenosine-stress/rest gated SPECT study using ^{99m}Tc-sestamibi and had normal perfusion on their scan. Of those, 27 patients (4.6%) were lost to follow-up leaving a final study cohort of 560 patients. Table 1 shows the baseline characteristics of these patients.

History of CAD was confirmed in 229 of the 560 patients (41%) by the presence of documented prior myocardial infarction or the documentation of CAD by coronary angiography of which 72% required coronary revascularization.

ECG changes suggestive of ischemia (ST-depression ≥ 1 mm of horizontal or downsloping depression

Table 1. Patients' baseline characteristics (*n* = 560)

Variables

Age (year)[a]	60 ± 11
Male, *n* (%)	234 (42%)
Family history of CAD, *n* (%)	35 (6%)
Known history of CAD, *n* (%)	229 (41%)
Smoking, *n* (%)	100(18%)
Hypertension, *n* (%)	423 (76%)
Diabetes, *n* (%)	263 (47%)
Dyslipidemia, *n* (%)	368 (66%)
Functional parameters[a]	
Rest LVEF	66 ± 11
Post-stress LVEF	65 ± 11
Rest LVEDV (ml)	93 ± 34
Post-stress LVEDV (mL)	95 ± 34
Rest LVESV (mL)	36 ± 27
Post-stress LVESV (mL)	36 ± 25
TID ratio	1.05 ± 0.15
Baseline heart rate (beats/min)	74 ± 14
Peak heart rate (beats/min)	89 ± 16
HRR (%)	23 ± 18
Medications	
Beta-blocker	303 (54%)
ACE-Inhibitor	98 (18%)
Angiotensin 2 receptor blocker	130 (23%)
Calcium channel blocker	107 (19%)
Statin	338 (60%)
Diuretic	92 (16%)

TID transient ischemic dilatation ratio, *HRR* heart rate response
[a]Mean ± SD

of the ST-segment 80 ms after the J-point) were seen in only 11% of the patients. No ST-elevation was observed.

Post-stress Change in LVEF and LV Volumes

Change in LVEF was normally distributed (*P* = 0.13 based on Shapiro's test indicting lack of departure from normality). The mean (± SD) change in LVEF was − 0.8% ± 5.3% (range; − 18% to 18%). Two hundred ninety-one patients (52%) had > 0% reduction vs. 221 (39%) with > 0% increase in LVEF. Forty-eight patients (9%) had no change in their LVEF. Hundred and thirty-five patients (24.1%) had ≥ 5% reduction vs 86 (15%) with ≥ 5% increase in LVEF and 28 patients (5%) had ≥ 10% reduction vs 14 (2.5%) with ≥ 10% increase in LVEF.

Tables 2 and 3 show the distribution of clinical, perfusion and functional parameters in patients with LVEF reductions of ≥ 5% and ≥ 10% as compared to those with < 5% and < 10% reduction.

The mean post-stress LVEF reduction in the 135 patients with ≥ 5% reduction was − 7.7 ± 2.6% (range − 5 to − 18%), whereas the mean post-stress LVEF reduction in the 28 patients with ≥ 10% reduction was − 11.6 ± 1.9% (range − 10 to − 18%).

In patients with ≥ 5% reduction in LVEF, the mean post-stress LVEDV was 94 ± 31 mL, not significantly different from the mean rest LVEDV of 90 ± 31 mL (*P* = 0.19). In contrast, the mean post-stress LVESV was significantly higher than the mean rest LVESV (39 ± 24 vs 32 ± 23 mL; *P* < 0.001). Thus, the ≥ 5% LVEF reduction was due to an increase in LVESV rather than a decrease in LVEDV. Similar findings were seen in patients with ≥ 10% LVEF reduction. In patients without ≥ 5% or ≥ 10% LVEF reduction, no significant change was noted in either LVEDV or LVESV following adenosine stress (*P* = 0.27-0.56).

Predictors of Post-stress Reduction in LVEF

In univariate analysis, among age, gender, family history of CAD, known history of CAD, smoking, hypertension, diabetes, rest LVEF, rest LVEDV, rest LVESV, post-stress LVEF, post-stress LVEDV, post-stress LVESV, TID ratio, baseline HR, peak HR and HRR, only known history of CAD, rest LVEF, post-stress LVEF, rest LVESV, post-stress LVESV and TID ratio were significantly associated with LVEF reduction of ≥ 5% (Table 2). Rest LVEF, post-stress LVEF and rest LVESV were significantly associated with LVEF reduction of ≥ 10% (Table 3).

There was no difference in HRR post-adenosine between patients with ≥ 5% or ≥ 10% reduction in LVEF vs those without such reductions (*P* = 0.99 and 0.11, respectively). Blunted HRR defined as < 20% maximum percent change in baseline heart rate was seen in 50% of patients with ≥ 5% vs 49% of patients with < 5% reduction in LVEF (*P* = 0.88). Similarly, there was no relationship between blunted HRR and reduction in LVEF of ≥ 10% (27% in patients with ≥ 10% vs. 50% in patients with < 10% reduction, *P* = 0.22). Finally, no significant association was found between adenosine-induced ischemic ST-depression and LVEF reduction of ≥ 5%; 15% of those patients had ischemic ST-depression vs 10% inpatients without ≥ 5% reduction (*P* = 0.32). There was also no significant difference (*P* = 0.11) in the rate of adenosine-induced ischemic ST-depression between patients with and without ≥ 10% LVEF reduction.

Table 2. Distribution of clinical and functional parameters in patients with LVEF reduction of $\geq 5\%$ as compared to the absence this reduction

	LVEF reduction < 5% (n = 425)	LVEF reduction ≥ 5% (n = 135)	P value	OR [95% CI]
Clinical parameters				
Age[a]	60 ± 11	62 ± 11	0.13	1.00 [1.00-1.04]
Male gender, n (%)	180 (42%)	54 (40%)	0.63	0.91 [0.61-1.35]
Family history of CAD, n (%)	28 (7%)	7 (5%)	0.56	0.78 [0.33-1.82]
Known history of CAD, n (%)	164 (39%)	65 (48%)	0.05	1.48 [1.00-2.20]
Smoking, n (%)	74 (17%)	26(19%)	0.63	1.13 [0.69-1.86]
Hypertension, n (%)	314 (74%)	109 (81%)	0.10	1.48 [0.92-2.40]
Diabetes, n (%)	191 (45%)	72(53%)	0.09	1.40 [0.95-2.06]
Dyslipidemia, n (%)	273 (64%)	95(70%)	0.19	1.32 [0.87-2.01]
Functional parameters[a]				
Rest LVEF	64.5 ± 10.5	68.7 ± 10.6	< 0.001	1.04 [1.02-1.07]
Post-stress LVEF	65.9 ± 10.4	61.1 ± 10.3	< 0.001	0.96 [0.94-0.98]
ΔLVEF	1.4 ± 3.9	− 7.7 ± 2.6	< 0.001	–
Rest LVEDV (mL)	94 ± 34	90 ± 31	0.20	1.00 [0.99-1.002]
Post-stress LVEDV (mL)	96 ± 35	94 ± 31	0.81	1.00 [0.99-1.003]
Rest LVESV (mL)	37 ± 28	32 ± 24	0.01	0.99 [0.98-1.00]
Post-stress LVESV (mL)	36 ± 25	39 ± 24	0.01	1.01 [1.00-1.012]
TID ratio	1.04 ± 0.14	1.10 ± 0.14	0.01	12.3 [1.6-104.5]
Baseline heart rate (beats/min)	73.6 ± 14.4	74.5 ± 14.6	0.90	1.00 [0.98-1.03]
Peak heart rate(beats/min)	89.3 ± 16.6	89.2 ± 15.8	0.92	1.00 [0.98-1.01]
HRR (%)	23.0 ± 19.0	21.0 ± 16.0	0.55	0.99 [0.98-1.01]

OR [*95% CI*], odds ratio [95% confidence interval]; *TID*, transient ischemic dilatation ratio; *HRR* heart rate response
[a]Mean ± SD

At multivariate analysis performed with the significant variables by univariate analysis, only known history of CAD, rest LVEF and TID ratio were significant predictors of LVEF reduction of $\geq 5\%$ whereas only rest LVEF was a significant predictor of LVEF reduction of $\geq 10\%$ (Tables 4, 5).

Figure 1 shows the relationship between the rest LVEF and change in LVEF in all patients. Significant inverse correlation is found between the two variables ($r = - 0.26$, $P < 0.001$).

Predictors of Cardiac Events

After a mean follow-up period of 24.1 ± 11.0 months, 45 patients (8%) had a cardiac event, including 4 (0.7%) hard (2 cardiac deaths and 2 nonfatal MI) and 41(7.3%) soft events (35 revascularization and six congestive heart failure requiring hospitalization).

Table 6 shows the potential variables that may predict cardiac events in the study population. Among those variables, only known history of CAD, smoking,

post-stress LVEF and peak HR were significant predictors of future cardiovascular events. In contrast, change in LVEF as continuous variable or as a cutoff reduction of 5% or 10% was not a significant predictor ($P = 0.91$, 0.96 and 0.27, respectively).

There was no significant difference in HRR between patients with and without cardiac events (17.2 ± 15.8 vs 23.2 ± 18.4 beats/min; $P = 0.21$), and no significant association was found between blunted HRR and cardiac events; cardiac event rate was 12% in patients with blunted HRR vs 7% in those without HRR blunting ($P = 0.31$).

At multivariate analysis, only known history of CAD was a significant predictor of cardiac events ($P < 0.001$) (Table 7).

Post-stress Reduction in LVEF and Cardiac Events

Eleven of the 135 patients (8.1%) who had $\geq 5\%$ reduction in their LVEF had cardiac events (0% hard, 8.1% soft). The soft events included ten

Table 3. Distribution of clinical and functional parameters in patients with LVEF reduction of ≥ 10% as compared to the absence this reduction

	LVEF reduction < 10% (n = 532)	LVEF reduction ≥ 10% (n = 28)	P value	OR [95% CI]
Clinical parameters				
Age[a]	60 ± 11	63 ± 10	0.38	1.02 [0.98-1.06]
Male gender, n (%)	223 (42%)	11 (39%)	0.78	0.90 [0.41-1.95]
Family history of CAD, n (%)	33 (6%)	2 (7%)	0.69	1.16 [0.26-5.11]
Known history of CAD, n (%)	214 (40%)	15 (54%)	0.16	1.71 [0.80-3.68]
Smoking, n (%)	96 (18%)	4 (14%)	0.80	0.77 [0.26-2.23]
Hypertension, n (%)	403 (76%)	20 (71%)	0.60	0.80 [0.34-1.86]
Diabetes, n (%)	246 (46%)	17 (61%)	0.13	1.80 [0.83-3.91]
Dyslipidemia, n (%)	347 (65%)	21 (75%)	0.29	1.60 [0.67-3.83]
Functional parameters[a]				
Rest LVEF	65.1 ± 10.6	72.8 ± 8.8	< 0.001	1.09[1.04-1.14]
Post-stress LVEF	64.9 ± 10.7	61.1 ± 8.6	0.02	0.97 [0.94-1.00]
ΔLVEF	− 0.2 ± 4.8	− 11.6 ± 1.9	< 0.001	–
Rest LVEDV (mL)	94 ± 34	82 ± 20	0.11	0.99 [0.97 -1.00]
Post-stress LVEDV (mL)	96 ± 35	86 ± 22	0.20	0.99 [0.98-1.00]
Rest LVESV (ml)	36 ± 28	23 ± 11	< 0.001	0.95 [0.92-0.98]
Post-stress LVESV (mL)	37 ± 25	34 ± 14	0.72	0.99 [0.97-1.01]
TID ratio	1.05 ± 0.15	1.06 ± 0.10	0.60	1.44 [0.02-68.7]
Baseline heart rate (beats/min)	73.8 ± 14.6	73.1 ± 10.6	> 0.99	1.00 [0.95-1.04]
Peak heart rate (beats/min)	89.0 ± 16.5	94.9 ± 14.7	0.31	1.02 [0.98-1.06]
HRR (%)	22.1 ± 18.2	30.9 ± 18.3	0.10	1.02 [0.99-1.05]

OR [95% CI], odds ratio [95% confidence interval]; *TID,* transient ischemic dilatation ratio; *HRR,* heart rate response
[a]Mean ± SD

revascularization and one congestive heart failure requiring hospitalization. Thirty-four of the 425 patients (8%) with < 5% LVEF reduction had cardiac events, including 4 (1%) hard (two cardiac deaths and two nonfatal MI) and 30(7%) soft events (25 revascularization and five congestive heart failure requiring hospitalization). No significant differences in the hard, soft or total cardiac event rates were found between the patients with and without ≥ 5% LVEF reduction (P = 0.58, 0.82 and > 0.99, respectively; Fig. 2A). There were also no significant differences in the hard, soft or total cardiac event rates between patients with ≥ 10% vs. those with < 10% reduction in LVEF (P > 0.99, = 0.14 and = 0.27, respectively; Fig. 2B).

Figure 3A and B show the unadjusted and adjusted Kaplan-Meier event-free survival curves in the patients with and without ≥ 5% and ≥ 10% LVEF reductions.

Event-free survivals were similar in patients with ≥ 5% reduction in LVEF and those without such reduction (P = 0.8). The unadjusted hazard ratio (95% confidence intervals) for cardiac events was 1.09 (0.55-2.15), P = 0.81, while the hazard ratio adjusted for the variables of known history of CAD, smoking, post-stress LVEF and peak HR was 0.87 (0.44-1.75), P = 0.71.

There were also similar event-free survivals in patients with ≥ 10% reduction in LVEF and those without such reduction (P = 0.2). The unadjusted hazard ratio for cardiac events was 1.84 (0.66-5.18), P = 0.25, while the hazard ratio adjusted for the variables of known history of CAD, smoking, post-stress LVEF and peak HR was 1.48 (0.52-4.3), P = 0.46.

DISCUSSION

To our knowledge, this study is the largest reporting on the frequency of LVEF reduction and its prognostic significance in patients who underwent adenosine stress imaging and had normal perfusion on their scan.[5,13,28]

In the current investigation, about 24% of patients with normal perfusion on adenosine stress imaging had ≥ 5% reduction in their LVEF following adenosine, which is generally considered significant.[8,9,17,23] A similar proportion of patients (22%) had such reduction in the study by Ferro et al. albeit in diabetic patients with normal perfusion following exercise or dipyridamole stress.[9] Brinkman et al reported an even higher percentage of patients (36.5%) with normal perfusion and ≥ 6% LVEF reduction post-adenosine suggesting that

Table 4. Multivariate analysis for possible predictor variables of LVEF reduction of $\geq 5\%$

Variable	P value	OR	95% CI	
			LL	UL
Known CAD	0.01	1.68	1.12	2.54
Rest LVEF	< 0.001	1.05	1.02	1.07
Rest LVESV (mL)	0.97	1.00	0.99	1.01
TID ratio	0.02	12.55	1.59	106

OR, odds ratio; [95% CI], [95% confidence interval]; TID ratio, transient ischemic dilatation ratio

Table 5. Multivariate analysis for possible predictor variables of LVEF reduction of $\geq 10\%$

Variable	P value	OR	95% CI	
			LL	UL
Rest LVEF	0.001	1.10	1.03	1.16
Rest LVESV (mL)	0.90	1.00	0.96	1.01

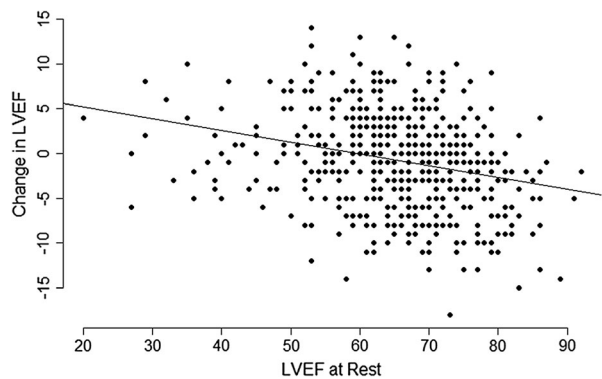OR, odds ratio; [95% CI], [95% confidence interval]

Figure 1. Plot of the change in LVEF against rest LVEF in all patients showing a significant inverse correlation between the two variables ($r = -0.26$, $P < 0.001$).

significant reductions in LVEF ($\geq 5\%$) are relatively common in patients undergoing adenosine-stress who have normal perfusion on their scan.[28]

Factors Affecting Reduction in LVEF

Multivariate analysis of the factors determining post-adenosine reduction in LVEF of $\geq 5\%$ showed that rest LVEF, known history of CAD and the TID ratio

were the only independent predictors of such reduction. In Ferro's study involving only diabetic patients, rest LVEF was also found to be an independent predictor of $\geq 5\%$ LVEF reduction.[9] The association of TID ratio with LVEF reduction is expected and explained by the fact that the post-stress LVEF reduction resulted in increased post-stress LV volumes (primarily LVESV) compared with rest, thereby increasing the TID ratio. The association between prior CAD and LVEF reduction may be related to occult coronary microvascular dysfunction (CMD) in these patients with presumably multiple risk factors, including diabetes and hypertension. In fact, diabetes has been reported to result in loss in contractile reserve, presumably due to CMD despite absence of significant CAD.[29-32]

LVEF Reduction Post-adenosine Stress and Cardiac Events

Perhaps the most important finding of our study is that, in patients with normal perfusion a post-adenosine LVEF reduction, regardless whether $\geq 5\%$ or $\geq 10\%$ was not associated with increased cardiac events. Lack of association between post-exercise or post-dipyridamole reduction in LVEF and cardiac events was previously reported by Marcassa et al and a similar conclusion was reached by Gomez et al using regadenoson when testing both $\geq 5\%$ and $\geq 10\%$ cutoff reductions in LVEF in patients with and without ischemia.[23,33] Interestingly, Ferro et al also reported that their diabetic patients with normal stress perfusion who had $\geq 5\%$ LVEF reduction following exercise or dipyridamole had similar event-free survival to those without such reduction.[9]

Only one SPECT study using ^{99m}Tc-sestamibi with exercise or dipyridamole stress reported lower cardiac event-free survival in patients without-stress induced ischemia who had post-stress reduction in LVEF of $\geq 5\%$ compared with those without such reduction. However, this study was small, involving only 114 patients of whom the majority (63%) underwent exercise rather than vasodilator stress.[8]

Proposed Mechanisms of LVEF Reduction Post-adenosine

Considering the lack of prognostic significance of post-stress LVEF reduction in patients with normal perfusion in our and in most other studies, it is intriguing to speculate about the mechanism(s) of such reduction. It seems unlikely that the LVEF reduction is due to post-ischemic myocardial stunning caused by ''balanced'' global ischemia not apparent on the perfusion scan considering the similar cardiac event rates (both hard

Table 6. Univariate predictors of cardiac events

	Without cardiac events (*n* = 515)	With cardiac events (*n* = 45)	*P* value	OR [95% CI]
Clinical parameters				
Age[a]	60 ± 11	60 ± 12	0.87	1.00 [0.97-1.03]
Male gender, *n* (%)	211 (41%)	23 (51%)	0.19	1.51 [0.82-2.77]
Family History of CAD, *n* (%)	32 (6%)	3 (7%)	0.75	1.08 [0.32-3.67]
Known history of CAD, *n* (%)	196 (38%)	33 (73%)	< 0.001	4.48 [2.26-8.87]
Smoking, *n* (%)	86 (17%)	14 (31%)	0.01	2.25 [1.15-4.41]
Hypertension, *n* (%)	387 (75%)	36 (80%)	0.47	1.32 [0.62-2.82]
Diabetes, *n* (%)	238 (46%)	25 (56%)	0.23	1.45 [0.79-2.68]
Dyslipidemia, *n* (%)	333 (65%)	35 (78%)	0.08	1.91 [0.93-3.95]
Functional parameters[a]				
Rest LVEF	68.8 ± 10.5	62.4 ± 11.8	0.09	0.97 [0.95-1.00]
Post-stress LVEF	65.0 ± 10.5	61.5 ± 11.3	0.05	0.97 [0.95 - 1.00]
Rest LVEDV (mL)	93 ± 34	97 ± 35	0.46	1.00 [0.99-1.01]
Post-stress LVEDV (mL)	95 ± 34	102 ± 39	0.19	1.00 [0.99-1.01]
Rest LVESV (mL)	36 ± 28	39 ± 27	0.27	1.00 [0.99-1.01]
Post-stress LVESV (mL)	36 ± 25	42 ± 29	0.11	1.01 [1.00-1.02]
TID ratio	1.05 ± 0.15	1.06 ± 0.15	0.93	1.35 [0.05-26.8]
Baseline heart rate (beats/min)	74.3 ± 14.6	69.5 ± 11.7	0.16	0.98 [0.94-1.01]
Peak heart rate (beats/min)	90.2 ± 16.3	81.0 ± 14.8	0.02	0.96 [0.93-0.99]
HRR (%)	23.1 ± 18.4	17.2 ± 15.8	0.22	0.98 [0.95-1.01]
Δ LVEF	− 0.8 ± 5.3	− 0.9 ± 5.4	0.91	1.00 [0.94-1.05]
< 5% reduction, *n* (%)	391 (76%)	34 (76%)	0.96	
≥ 5% reduction, *n* (%)	124 (24%)	11 (24%)		1.02 [0.50-2.07]
< 10% reduction, *n* (%)	491 (95%)	41 (91%)	0.27	
≥ 10% reduction, *n* (%)	24 (5%)	4 (9%)		2.00 [0.66-6.03]

OR [95% CI], odds ratio [95% confidence interval]; *TID*, transient ischemic dilatation ratio; *HRR*, heart rate response
[a]Mean ± SD

Table 7. Multivariate analysis for possible predictor variables of cardiac events

			95% CI	
Variable	*P* value	OR	LL	UL
Known history of CAD	< 0.001	3.74	1.90	7.83
Smoking	0.19	1.61	0.76	3.25
Post-stress LVEF	0.41	0.99	0.96	1.02
Peak heart rate (beats/min)	0.08	0.97	0.95	1.00

OR, odds ratio; *[95% CI]* [95% confidence interval]

and soft) observed in our patients with and without a significant post-stress LVEF reduction and the lack of any hard cardiac events in the former patients after a mean follow-up of 2 years. In fact, a previous report by Supino et al showed that in patients with 3-vessel disease treated only medically the hard event rate (cardiac death or nonfatal MI) in those with ≥ 5% post-exercise reduction in LVEF was about 5% per year

(2.8% with 0 to 7% LVEF reduction and 6.9% with ≥ 8% LVEF reduction) or about 10% over 2 years.[34] Thus, we would have expected a hard event rate of about 10% in two years in our patients with ≥ 5% LVEF reduction (of whom about half had ≥ 8% LVEF reduction) if those patients truly had 3-vessel CAD (or ≥ 50% left main stenosis) and our sample size would have sufficed to detect this rate. In
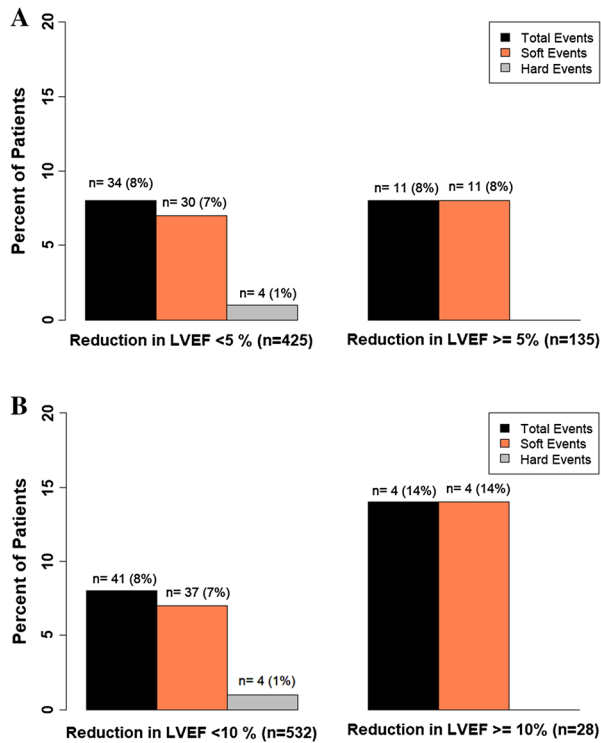
Figure 2. A Total, soft and hard cardiac event rates in the patients with ≥ 5% post-adenosine reduction in LVEF vs those in the patients without such reduction. **B** Total, soft and hard cardiac event rates in the patients with ≥ 10% post-adenosine reduction in LVEF vs those in the patients without such reduction.

Figure 3. A Unadjusted and adjusted Kaplan-Meier event-free survival curves in the patients with and without ≥ 5% post-adenosine reduction in LVEF showing similar event-free survivals in both groups of patients ($P = 0.8$). **B** Unadjusted and adjusted Kaplan-Meier event-free survival curves in the patients with and without ≥ 10% post-adenosine reduction in LVEF showing similar event-free survivals in both groups of patients ($P = 0.2$).

our study, no hard cardiac events were observed in any patient with ≥ 5% or ≥ 10% reduction although all of these patients underwent medical treatment only following the index scan. Another noteworthy observation is that although just nine of our patients with ≥ 5% LVEF reduction underwent diagnostic coronary angiography based on a clinical indication other than the adenosine scan result, only one had severe/extensive CAD (defined a ≥ 50% left main stenosis or ≥ 70% stenosis of the LAD, circumflex and RCA or their major branches), not significantly different from the 2 of 31 patients with < 5% LVEF reduction who also underwent diagnostic coronary angiography.

Potential explanations include measurement errors in determining the LVEF using the QGS program that may exceed 4% in some patients which may be the case with high background activity adjacent to the myocardium and marked attenuation-related defects (breast and/or diaphragmatic attenuation artifacts) resulting in inaccurate endocardial tracking with overestimation of LVESV and underestimation of LVEF akin to one of the proposed mechani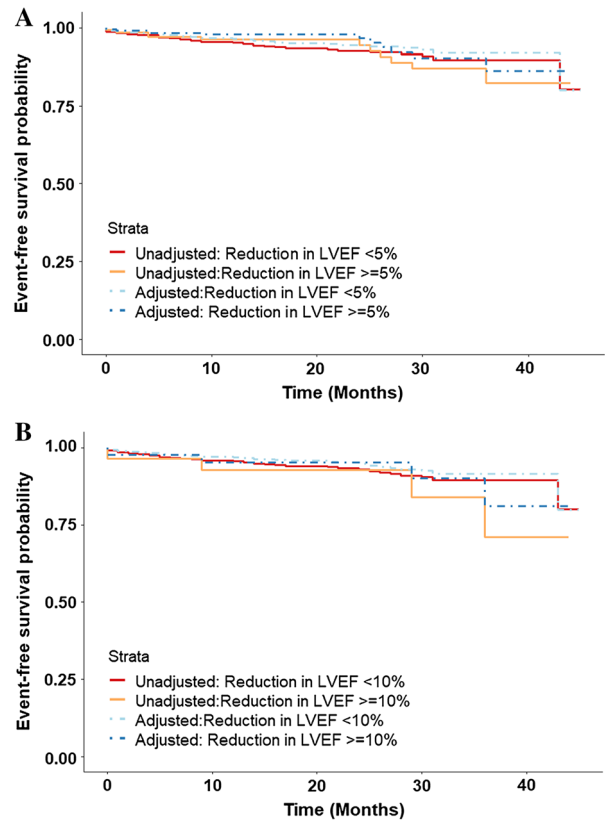sms of measured decreased LVEF in patients with severe true perfusion defects.[5,16] The reproducibility of LVEF measurement at our institution measured by two operators and by one operator at two different times was within 4.4%, which is similar to the 5.2% reproducibility of LVEF measurement determined by Johnson et al who considered only a reduction greater than 5% (i.e., ≥ 6%) as significant.[10] To account for potentially higher measurement errors, we examined a higher threshold of a significant reduction in LVEF of ≥ 10% with no change in overall study conclusions.

Although the change in LVEF in the overall cohort was essentially normally distributed with only a very small shift to the right, the somewhat higher percentage of patients with LVEF reduction compared with LVEF increase suggests that there may a ''real'' effect behind the more frequent LVEF reductions.

One possible mechanism could be autonomic dysfunction, especially in patients with diabetes who comprised about half of our patients. Heart rate response

(HRR) post-adenosine can serve as a simple marker of autonomic dysfunction but, in our study, there was no difference in HRR between patients with $\geq 5\%$ or $\geq 10\%$ reduction in LVEF vs those without such reductions. Moreover, HRR blunting, defined as $< 20\%$ maximum percent change in baseline heart rate was seen in almost equal proportions of patients with $\geq 5\%$ and $< 5\%$ reduction in LVEF with no significant difference in HRR blunting between patients with $\geq 10\%$ vs $< 10\%$ reduction in LVEF although the sample sizes for the latter comparison is quite small.

We can only speculate about other possible mechanism(s) for the observed LVEF reductions in patients with normal perfusion but CMD in patients with known CAD, diabetes and, potentially in the elderly may have contributed to this phenomenon.[29-32]

LIMITATIONS

One of the limitations of our study is its retrospective nature and that it was conducted at a single institution. We did not have a sufficient number of patients who underwent coronary angiography to draw firm conclusions regarding the presence of severe and/or extensive CAD in patients with significant post-stress reduction in LVEF vs those without because patients with normal perfusion typically do not undergo coronary angiography unless other findings are present compelling the cardiologist to perform coronary angiography. Reduction in LVEF with normal perfusion is also normally not an indication for coronary angiography without other compelling findings. This was one of the main reasons for using cardiac events as the primary endpoint in our study. Due to the retrospective nature of the study, we could not study the post-stress reduction in LVEF at more than one timepoint, for example at 30 min, 1 and 2 h to determine the time of peak decline in LVEF and eventual recovery in patients who showed LVEF reduction. Finally, despite our sample size being the largest to date in this particular patient population, it is insufficient to detect small differences in outcome rates considering that those are quite low. Yet, our study can be considered as hypothesis-generating and might lead to larger studies for further investigation and confirmation.

NEW KNOWLEDGE GAINED

Significant ($\geq 5\%$) and even marked ($\geq 10\%$) reductions in LVEF following adenosine do not seem to be associated with adverse prognosis compared with patients without such reduction when the stress/rest gated adenosine SPECT study is normal. The post-adenosine LVEF reduction in this setting is probably not related to ''balanced ischemia'' and is likely to be seen more often in patients with known CAD and those patients with higher rest LVEF.

CONCLUSION

The present study showed that significant post-adenosine stress reduction in LVEF does not confer an adverse prognosis and is not an independent prognosticator in patients with normal perfusion on ^{99m}Tc-sestamibi myocardial perfusion scan. However, due to the relatively small sample size of our study and the relatively low event rates, our study conclusions are preliminary and need to be supported by larger studies. If confirmed, this may have implications in management of patients with normal perfusion and normal LVEF on their post-stress scan.

Disclosure

The authors have no conflicts of interest to report.

Author Contributions

OSO, MEJ: contributed to the conception and design of the study, analysis and interpretation of data, drafting and final approval of the manuscript. AA, BB, OA, MA, HZ, OA, MAJ, SJ, HJ, OA, OA: actively involved in collecting and analyzing data and approved the of final manuscript.

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