Impact of imaging protocol on left ventricular ejection fraction using gated-SPECT myocardial perfusion imaging

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Background. **There are limited data on the impact of the imaging protocol (single-day stress-rest, SD, vs. dual-day, DD) on the change in left ventricular (LV) ejection fraction (EF) (post-stress-rest) in relation to ischemia and on outcome.**

Methods. **Using propensity score matching procedure, 490 of 1121 patients with known CAD, undergoing a SD or a DD in a multicenter study, were evaluated. Stress and rest gated-SPECT myocardial perfusion imaging was used to quantify LV perfusion, EF, and volumes. Outcome was assessed at an average follow-up time of 3.2 years.**

Results. **Post-stress LVEF in SD and DD were comparable across all degrees of ischemia. The change in LVEF in patients with severe ischemia was, however, higher in the DD protocol, independent of the extent of CAD. At follow-up, 240 patients (49.0%) required coronary revascularization (CR) and 52 patients (10.6%) had hard events. The ischemic burden was independently associated with CR and hard-events; the post-stress LVEF was associated with CR but the change in EF was not predictive of either CR or hard events.**

Conclusions. **In patients with severe ischemia, underestimation of post-stress myocardial stunning could be observed with the SD protocol. Post-stress LVEF and the extent ischemia, but not the change in EF, are predictive of CR and hard events. (J Nucl Cardiol 2017;24:1292–301.)**

Key Words: Gated-SPECT • myocardial perfusion imaging • prognosis • study protocol

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Abbreviations	
CAD	Coronary artery disease
CR	Coronary revascularization
DD	Dual-day
EF	Ejection fraction
EDV	End-diastolic volume
ESV	End-systolic volume
LV	Left ventricular
MPI	Myocardial perfusion imaging
SD	Single-day
SDS	Summed difference score
SRS	Summed rest score
SSS	Summed stress score

See related article, pp. 1302–1304

INTRODUCTION

Gated-SPECT myocardial perfusion imaging (MPI) provides incremental diagnostic and prognostic information in patients with known or suspected coronary artery disease (CAD).[1–5] The use of 99mTc-labeled tracers, due to their intra-cellular trapping, requires two separate tracer injections for a complete stress/rest study; this can be obtained using a single-day (SD) or dual-day (DD) protocols.[6] The time interval between tracer injection during stress and image acquisition, the type of stressor used (exercise vs vasodilator stress), and the study protocol could affect the relationship between ischemia and left ventricular (LV) ejection fraction (EF) and conceivably outcome prediction.[7–9]

The aim of this study was to examine the differential impact of these variables on myocardial perfusion and LV EF and volumes using a propensity matching analysis of a large cohort of patients enrolled in a multicenter study in whom coronary angiographic data were also available.

METHODS

The study cohort included patients aged >18 years with known or suspected CAD who underwent stress/rest gated-SPECT imaging with either SD or DD protocol for clinical indications in six institutions in Italy. At each site, patients were retrospectively selected from the respective databases according to the following inclusion criteria: stable sinus rhythm and coronary angiography performed within 3 months from the gated-SPECT. Patients were excluded if they had pacemakers, previous coronary revascularization (CR) or moderate-to-severe valvular disease. In each of the recruiting institutions, a physician trained in nuclear cardiology collected data on demographics, risk factors, and clinical presentation. The type of stress (either exercise or pharmacological) was based on the discretion of the physician performing the study. The study protocol (SD or DD) and the radiopharmaceutical used were according to the local practices at each site. An informed written consent was obtained from all patients.

Gated-SPECT acquisition and interpretation

Stress and rest perfusion images were analyzed locally and semi-quantitatively scored according to the 17-segment model[10] and a 5-point scale (from 0 = normal to 4 = absence of detectable tracer uptake) with an automated software program (QPS).[10] The summed stress score (SSS) and summed rest score (SRS) were calculated by adding the scores of the 17 segments in the stress and rest images, respectively. SSS was classified as follows: <4: Normal; 4–8: Mildly abnormal; 9–13: Moderately abnormal; >13: Severely abnormal. The summed difference score (SDS = SSS-SRS) was used as a marker of ischemia, and classified as follows: <2: No ischemia; 2–4: Mild ischemia; 5–8: Moderate ischemia; >8: Severe ischemia. Left ventricular volumes and EF were measured after stress and at rest using a previously validated software (QGS).[11] The LVEF, end-systolic volume (ESV), and end-diastolic volume (EDV) after stress and at rest were calculated at each institution. Transient ischemic dilatation was based on gated EDV and ESV.[12]

Coronary angiography was performed using standard techniques; >50% luminal diameter narrowing was considered significant stenosis.

Events during the follow-up were defined as the need for percutaneous or surgical CR due to worsening symptoms or hard events, defined as the occurrence of cardiac death or acute coronary syndrome. These events were verified by review of hospital records, interviewing patients, their family members or treating physicians.

Statistical Analysis

Continuous data are presented as mean ± 1 standard deviation. Categorical variables are presented as numbers or proportions and were compared with the continuity corrected Chi-square or Fischer's-exact test, as appropriate. Patients undergoing a SD or a DD protocol were balanced using the propensity score matching procedure. Rosenbaum and Rubin first proposed this method to balance the variables related to the choice of the exposure (treatment) in order to reconstruct a situation similar to a random assignment.[13] The propensity score model was generated using all potential covariates that could affect the group allocation, in order to draw more reliable results. A non-parsimonious logistic model was used to estimate the individual probability to undergo a SD or a DD study protocol for each patient. The matching procedure used in this analysis was to match cases in the SD and DD group by similarity of propensity score. A 1:1 matching procedure without replacement was used. The impact of the study protocol and amount of ischemia combinations on the LV stress/rest EF changes was assessed by a two-way principal analysis ANOVA. Two models were explored. In the first

model, as independent variables (factors) were considered the study protocol and amount of ischemia; in the second model, the presence and extent of CAD were additional factors. The LVEF changes were considered as the dependent variable in all models. A post hoc test (Scheffé F test) was performed to identify the main sources of variability. If a significant F value was found for one independent variable, then this was referred as a main effect. When a main effect was found, then a post hoc test (Scheffé test) was performed to compare the dependent variable upon the levels of the factor, thus identifying the main sources of variability. A multinomial logistic regression analysis was performed, to identify independent predictors of

Table 1. Characteristics of the study cohort

	Tetro SD	Mibi SD	Mibi DD	*P*
N	525	151	445	
Age	64.5 ± 9.9	64.0 ± 9.5	66.6 ± 8.9	.001
Gender, *M*, *n* (%)	388 (73.9)	85 (56.2)	316 (71.1)	.0002
Stressor, *n* (%):				<.0001
Exercise	406 (77.3)	101 (66.9)	222 (49.9)	
Dipyridamole	119 (22.7)	50 (33.1)	223 (50.1)	
Coronary angiography, *n* (%)				<.0001
No CAD	233 (44.4)	15 (9.9)	95 (21.3)	
Single vessel disease	132 (25.1)	6 (4.0)	68 (15.3)	
Multi-vessel disease	160 (30.5)	130 (86.1)	282 (63.4)	
Coronary risk factors, *n* (%)				
Hypertension	301 (57.3)	115 (76.1)	294 (66.1)	<.001
Hypercholesterolemia	304 (57.9)	80 (52.9)	220 (49.4)	.03
Diabetes mellitus	118 (22.5)	122 (80.8)	95 (21.3)	<.001
Previous MI, *n* (%)	15 (2.9)	30 (19.9)	154 (34.6)	<.0001
Delay injection-stress acquisition (min)	16.5 ± 5.0	28.6 ± 3.5	37.9 ± 8.2	All <.001

CAD coronary artery disease, *%HR* percentage of maximal age-predicted heart rate, *MI* myocardial infarction

Table 2. Clinical findings in the study cohort before and after propensity matching

	Before Matching			After Matching		
	Tetro SD	MIBI DD	*P*	Tetro SD	MIBI DD	*P*
N	525	445		245	245	
Age	64.5 ± 9.9	66.6 ± 8.9	.007	66.0 ± 9.5	67.1 ± 8.6	.18
Gender, *M*, *n* (%)	388 (73.9)	316 (71.1)	.31	192 (78.4)	179 (73.2)	.11
Stressor, *n* (%):			<.0001			.97
Exercise	406 (77.3)	222 (49.9)		142 (57.9)	143 (58.1)	
Dipyridamole	119 (22.7)	223 (50.1)		103 (42.1)	102 (41.9)	
Exercise %HR	83.2 ± 10.4	83.0 ± 10.5	0.25	81.2 ± 0.9	83.7 ± 10.0	.17
Coronary angiography, *n* (%)			<.0001			.29
No CAD	233(44.4)	95 (21.3)		75 (30.6)	74 (30.1)	
Single vessel disease	132 (25.1)	68 (15.3)		41 (16.8)	29 (11.9)	
Multi-vessel disease	160 (30.5)	282 (63.4)		129 (52.6)	142 (58.0)	
Coronary risk factors, *n* (%)						
Hypertension	301 (57.3)	294 (66.1)	<.006	160 (65.3)	159 (65.1)	.95
Hypercholesterolemia	304 (57.9)	220 (49.4)	.01	143 (58.4)	122(50.0)	.09
Diabetes mellitus	118 (22.5)	95 (21.3)	.57	47 (19.2)	42 (17.1)	.54
Previous MI, *n* (%)	15 (2.9)	154 (34.6)	<.0001	15 (6.1)	20 (8.1)	.48
Delay injection-stress acquisition (min)	16.5 ± 5	37.9 ± 8.2	<.001	17.0 ± 6.0	37.5 ± 7.5	<.001

CAD coronary artery disease, *%HR* percentage of maximal age-predicted heart rate, *MI* myocardial infarction

events, considering the occurrence of hard events or CR as dependent variables, with patients with ''no events'' as reference group. The χ^2 value, odds ratio (OR), corresponding 95% confidence interval (CI), and the Wald test *P* value are reported for each factor. Survival estimates for patients grouped according to the study protocol were calculated using the Kaplan–Meier method and compared by the log-rank test. To assess the incremental prognostic information from the addition of demographic, clinical, scintigraphic, and angiographic variables, data analysis was also performed according to a modified stepwise procedure in which individual factors were included in the model in the same order in which they would be considered in the clinical practice. Increment in information of the model at each step was considered significant when the log-likelihood difference had a *P* value <0.05. Statistical analysis was performed with Statistical Version 10 (StatSoft, Tulsa, USA. Propensity matching was performed with the MatchIt Package[14] for R (version 3.1.1).[15] A *P* value <0.05 (two-tailed) was considered significant.

RESULTS

The study cohort included 1121 patients with a mean age 65.1 + 9.6 years, of whom 70% were men. The SD stress/rest protocol was employed in 676 (60%) patients and the DD protocol in 445 (40%); 99mTc-tetrofosmin was used in 525 (47%) patients and 99mTc-sestamibi in 596 (53%). The tracer-protocol combinations employed as well as the respective pertinent clinical data are shown in Table 1. Tetrofosmin was exclusively used in conjunction with the SD protocol, while 75% of studies with sestamibi employed the DD protocol. The choice of the pharmaceutical was based on local practices and not upon patient demographics.

Patients undergoing the SD protocol were younger, mostly males, very few had a prior myocardial infarction and the majority were able to perform an exercise stress test. A multi-vessel disease was documented in 86% of

Table 3. Perfusion and function data in matched groups according to the type of protocol

Perfusion data	Tetro SD	Mibi DD	*P*
N	245	245	
SRS	2.2 ± 3.9	2.2 ± 4.5	.94
SSS	7.0 ± 5.0	6.5 ± 6.4	.26
SDS	4.9 ± 3.2	4.2 ± 4.2	.08
% Abnormal myocardium rest	3.2 ± 5.7	3.2 ± 6.6	.94
% Abnormal myocardium stress	10.4 ± 7.3	9.5 ± 9.4	.24
% Abnormal myocardium ischemic	7.1 ± 4.7	6.2 ± 6.2	.08
SSS category, *n* (%)			
Normal 0–3	53 (21.6)	75 (30.5)	<.0001
Mild 4–8	120 (49.0)	69 (28.0)	
Moderate 9–13	44 (18.0)	33 (13.4)	
Severe > 13	28 (11.4)	69 (28.1)	
SDS category, n (%)			
No ischemia 0–1	36 (14.7)	87 (35.4)	<.0001
Mild ischemia 2–3	82 (33.5)	56 (22.8)	
Moderate ischemia 4–7	96 (39.2)	65 (26.4)	
Severe ischemia >8	31 (12.6)	38 (15.4)	
Functional data			
LVEF rest (%)	53.8 ± 13.8	54.4 ± 14.1	.61
LVEF stress (%)	51.6 ± 13.9	51.8 ± 14.0	.88
stress/rest LVEF changes	−2.2 ± 4.9	−2.6 ± 6.7	.39
EDV index stress (cc/m^2)	65 ± 29	55 ± 24	<.001
ESV index stress (cc/m^2)	34 ± 25	29 ± 21	.02
EDV index rest (cc/m^2)	62 ± 28	54 ± 22	<.001
ESV index rest (cc/m^2)	32 ± 26	27 ± 19	.01
TID EDV	1.04 ± 0.1	1.05 ± 0.15	.43
TID ESV	1.10 ± 0.22	1.13 ± 0.28	.20

% Abnormal myocardium (stress and rest) was calculated by dividing the summed scores by 68, the maximum potential score (4 points × 17 segments), and multiplying by 100. The difference (stress-rest) indicates the % Abnormal Myocardium Ischemic
EDV end-diastolic volume, *EF* Ejection fraction, *ESV* end-systolic volume, *LV* left ventricle, *SDS* summed difference score, *SRS* summed rest score, *SSS* summed stress score, *TID* transient ischemic dilation

patients undergoing the SD protocol with sestamibi, while 44% of patients undergoing the SD tetrofosmin protocol had no significant CAD.

To avoid the influence of confounders on the analysis of the relation between the different study protocols, a propensity matching approach was used, with the exclusion of the group of patients undergoing the SD protocol with sestamibi, due to the smaller sample size ($n = 151$; Table 1). Clinical and angiographic data before and after matching are reported in Table 2. Though no significant differences were documented between the SD and the DD protocol in SSS, SRS, and SDS, patients undergoing the DD protocol more frequently showed either normal or severely abnormal results than patients undergoing the SD protocol (Table 3). No significant differences were documented between the two groups regarding rest and post-stress LVEF. However, stress and rest LV end-diastolic and end-systolic volumes were significantly higher in patients undergoing the SD protocol (Table 3).

Combined perfusion and function assessment

To better define the relative influence of the study protocol and the amount of ischemia on stress/rest LVEF changes, a two-way ANOVA was performed. In the first model, the amount of ischemia ($F = 6.02$; $P < .001$) and the study protocol ($F = 4.2$; $P = .041$) had a significant impact on the change in EF (stress test) while the type of stress was not (F = 0.04, P = NS). The LVEF and the change in EF varied according to the presence and severity of ischemia in the SD and DD protocols (Figure 1). Post hoc evaluation of the relative effect of the study protocol and the presence and severity of ischemia showed no significant differences in the group of patients who underwent the SD protocol; however, a significantly greater reduction in the LVEF was documented in patients with severe ischemia undergoing the DD protocol (Figure 2).

In the second model, including also extent and severity of CAD, the extent of ischemia remained to have a significant impact on the change in LVEF ($F = 5.0$, $P = 0.002$), while the presence ($F = 1.10$,

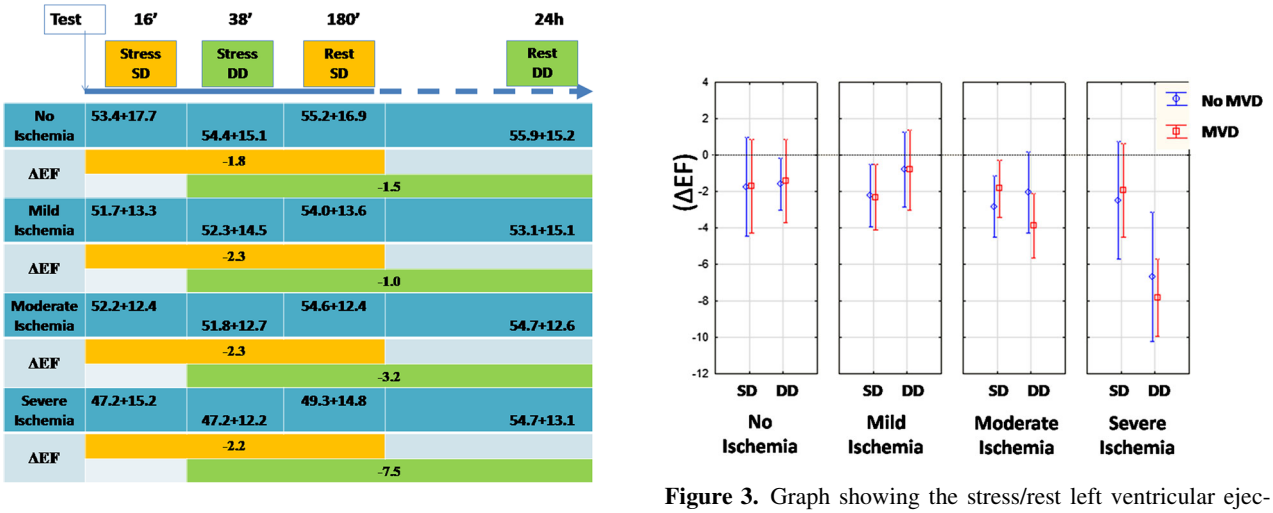

Figure 1. Schematic representation of the single-day (SD) and dual-day (DD) protocols, with associated test and acquisition average timings. Left ventricular ejection fraction values and stress/rest ejection fraction changes (ΔEF) are reported, according to the presence and severity of ischemia.

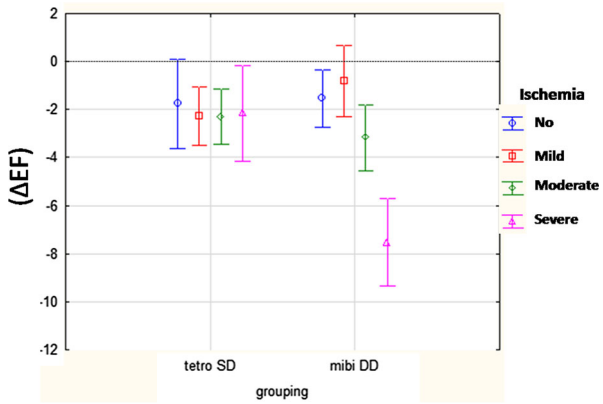

Figure 2. Graph showing the stress/rest left ventricular ejection fraction changes (ΔEF) according to the amount of ischemia in relation to the study protocol employed. *Vertical bars* denote 95% Confidence Intervals. *DD* Dual-day, *SD* Single-day.

Figure 3. Graph showing the stress/rest left ventricular ejection fraction changes (ΔEF) according to the amount of ischemia in relation to the study protocol employed and to the severity of coronary artery disease. *Vertical bars* denote 95% Confidence Intervals. *DD* Dual-day, *MVD* Multiple-vessel disease; *SD* Single-day.

$P = 0.29$) and severity of CAD ($F = 0.24$, $P = 0.62$) and the study protocol ($F = 2.85$, $P = 0.09$) were not (Figure 3).

The post-stress and rest LV volumes according to presence and severity of ischemia and the study protocol employed are reported in Table 4. Left ventricular volumes (EDV and ESV) increase with the worsening of ischemia both in the SD and DD protocol. Across the different amounts of ischemia, LV volumes are higher for the SD than for the DD protocol, both at rest and after stress. According to the two-way ANOVA, while the amount of ischemia is responsible for the increase in volumes (with the same trend in SD and DD), only the study protocol is the factor significantly associated to the differences in LV volumes within the same category of severity of ischemia, both post-stress and at rest.

Outcome data

During an average follow-up of 3.2 ± 2.1 years (range 8 days to 5.2 years) 240 patients (49.0% of the propensity matched patients) underwent CR and 52 patients (10.6%) had hard events. A comparable cumulative event rate was documented in the SD (55.3%) and in the DD (63.9%) groups ($P = 0.08$) (Figure 4).

Clinical and MPI data in those with and without events are shown in Table 5. Those with events were older, more likely men, have diabetes mellitus and multi-vessel CAD. Patients with hard events had higher SSS, EDV, and ESV, and lower rest and post-stress LVEF than patients with no events or undergoing CR (Table 5). Patients with undergoing CR had greater SDS and stress/rest LVEF changes than patients with no events (Table 5).

When the clinical and MPI variables that were significantly associated with events by univariate analysis were included in a multiple logistic regression analysis, the presence of multi-vessel CAD was the strongest variable associated with both hard events and CR (Table 6). Amongst the MPI variables, the SDS was independently associated with both CR and hard events, and the post-stress EF was associated with CR. The change in EF between post-stress and rest was not independently associated with either CR or hard events. When clinical, perfusional and functional scintigraphic data, and CAD extent were sequentially added in a stepwise model, gated-SPECT data had a significant incremental prognostic value for CR and hard events

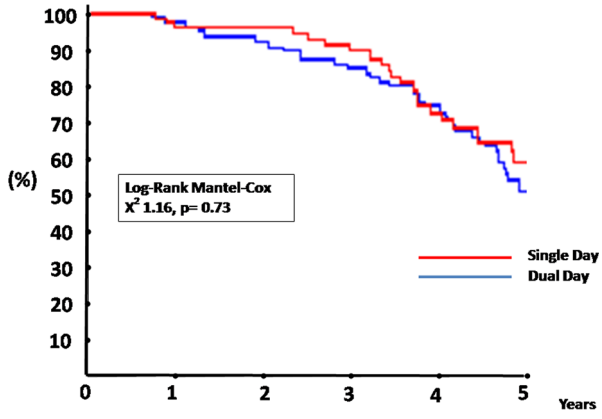

Figure 4. Kaplan-Meier survival estimates for patients grouped according to the study protocol.

Table 4. Left ventricular rest and post-stress end-systolic and end-diastolic volumes according to the study protocol

	Tetro SD	MIBI DD	Tetro SD	MIBI DD
	EDV rest ($F = 13.7$, <0.001)		EDV post-stress ($F = 12.1$, <0.001)	
No ischemia	117 ± 37	89 ± 46	117 ± 38	92 ± 48
Mild	119 ± 41	105 ± 59	122 ± 43	106 ± 59
Moderate	112 ± 36	100 ± 36	118 ± 39	105 ± 38
Severe	130 ± 62	110 ± 45	135 ± 64	119 ± 46
	ESV rest ($F = 7.3$, =0.007)		ESV post-stress ($F = 5.5$, =0.019)	
No ischemia	59 ± 33	45 ± 38	63 ± 56	47 ± 41
Mild	61 ± 32	55 ± 48	65 ± 53	57 ± 51
Moderate	60 ± 29	48 ± 28	63 ± 41	55 ± 33
Severe	74 ± 54	54 ± 36	99 ± 48	67 ± 39

Abbreviations as Table 3
Volumes are in ml
F values related to the study protocols as main effect

Table 5. Clinical and scintigraphic data according to the presence and type of events at follow-up

	No Events	Hard Events	Revasc	*P* value
N (%)	198 (40.4)	52 (10.7)	240 (49)	
Age (years)	64.4 ± 9.4	70.7 ± 8.5*$	66.7 ± 8.8	* vs Revasc; $ vs No events
Gender, *M*, *n* (%)	131 (66.1)	40 (76.1)	191 (79.6)	0.01
Study protocol §, *n* (%)				0.18
Single-day	109 (44.6)	23 (9.3)	113 (46.1)	
Dual-day	89 (36.1)	29 (12.0)	127 (51.8)	
Clinical findings, *n* (%)				
Previous MI	14 (6.9)	4 (8.1)	0	0.14
Multi-vessel disease	56 (28.2)	31 (69.6)	151 (63.0)	<0.0001
Risk factors, *n* (%)				
Hypertension	128 (64.4)	37 (71.7)	149 (62.1)	0.46
Diabetes mellitus	38 (14.9)	20 (39.1)	44 (18.5)	=0.001
Hypercholesterolemia	98 (49.4)	20 (39.1)	144 (60.2)	=0.01
Stressor, *n* (%)				=0.001
Exercise	94 (47.7)	26 (50.0)	158 (65.9)	
Dipyridamole	104 (52.3)	26 (50.0)	82 (34.1)	
Scintigraphic data				
SSS	5.9 ± 5.9	9.1 ± 6.1#*	7.6 ± 5.4$	#, $ vs no events; * vs Revasc.
SDS	3.4 ± 3.2*	5.4 ± 3.9	5.8 ± 3.9	* vs hard events and Revasc
Rest LVEF (%)	52.3 ± 14.7	46.1 ± 16.9$*	56.0 ± 11.1	$ vs Revasc; * vs No events.
Post-stress LVEF (%)	50.5 ± 14.7	44.2 ± 17.2$*	52.6 ± 11.7	$ vs Revasc; * vs No events.
Stress/rest LVEF changes	−1.8 ± 5.6	−1.9 ± 5.5	−3.4 ± 6.3*	* vs Hard events and No events
Rest EDV (ml)	116 ± 63	122 ± 58$	101 ± 37*	$ vs Revasc; * vs No events.
Rest ESV (ml)	62 ± 54	73 ± 56$*	47 ± 29*	$ vs Revasc; * vs No events
Post-stress EDV (ml)	120 ± 65	125 ± 59$*	106 ± 40*	$ vs Revasc; * vs No events.
Post-stress ESV (ml)	67 ± 57	78 ± 58$*	54 ± 33	$ vs Revasc; * vs No events.

§ Proportion of events according to the study protocol
Revasc: Revascularization. Other abbreviations as Table 3
For continuous variable, the "between groups" comparisons from ANOVA is shown. For categorical variables, the global Chi-square p value is reported
* $P < 0.05$; $ $P < 0.01$; # $P < 0.001$

over clinical variables; the addition of CAD information further improved the global χ^2 regarding CR but not for hard events (Figure 5).

DISCUSSION

This study evaluated the differential effects of 2 study protocols on the changes in LVEF (between post-stress and rest) and myocardial perfusion by gated-SPECT MPI using a propensity matching model in a large cohort of patients in whom the coronary anatomy was also defined by invasive coronary angiography.

Severe ischemia were higher in patients undergoing the DD protocol, independently of the extent of CAD. The type of stressor employed did not seem to influence the relationship between the amount of ischemia and LVEF changes.

Differences in the time interval between the stress tracer injection and image acquisition, and between

Table 6. Multinomial logistic regression analysis results, assessing independent factors predisposing to hard events or revascularization during follow-up; patients with no events are the reference group

	χ^2	Wald test *P* value	OR	95% CI
Outcome: hard events				
Variable				
Multi-vessel disease (y)	12.7	0.0004	4.45	1.93–10.12
Age*	10.8	0.001	1.08	1.03–1.14
Diabetes mellitus (y)	8.6	0.003	3.40	1.49–7.70
Summed difference score*	4.42	0.035	1.14	1.01–1.29
Outcome: revascularization				
Variable				
Multi-vessel disease (y)	17.9	<0.0001	2.92	1.78–4.81
Summed difference score*	16.82	<0.0001	1.23	1.11–1.35
Age (y)*	6.2	0.013	1.03	1.01–1.06
Gender, M	5.5	0.018	2.02	1.12–3.64
End-systolic volume*	5.4	0.021	0.987	0.975–0.998
Post-stress LV ejection fraction*	4.14	0.04	1.02	1.01–1.05

* As continuous variable
y yes

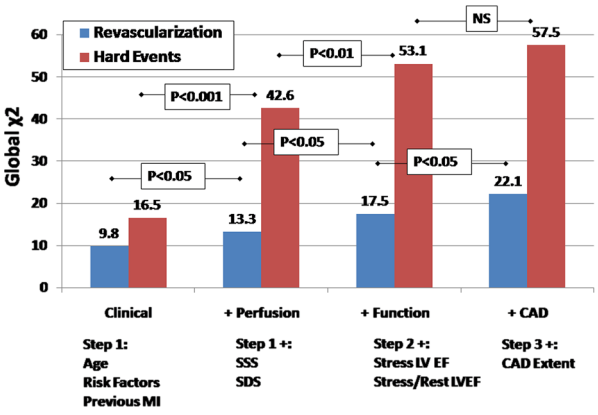

Figure 5. Bar graph illustrating the incremental prognostic value (depicted by the global χ^2 values on the *y*-axis) of perfusional (Summed Stress Scores, SSS, and Summed Difference Scores, SDS) and functional (Stress LVEF and Stress/Rest LVEF) over clinical data for coronary revscularization (CR) and hard events. The presence of significant coronary stenoses has a further significant incremental prognostic for CR, but not for hard events. *CAD* coronary artery disease; *LVEF* left ventricular ejection fraction; *MI* myocardial infarction.

stress and rest evaluation, might provide partial explanation to the observed data. In our study, the post-stress LVEF in the SD and the DD was comparable across all degrees of ischemia, despite the average time-interval between the stress test and images acquisition were shorter in the SD than in the DD (16 vs 38 min). However, rest LVEF in patients with severe ischemia in the DD group was higher than in the SD group, thus explaining the differences in the change in EF. The delay between the stress and rest imaging in the SD might be too short to ensure a complete functional recovery in patients with severe ischemia.

Despite these differences, all MPI variables were significantly associated with the events by univariate analysis; however, by logistic multinomial regression analysis, the post-stress EF and the SDS were independently associate with events, in both the SD or DD protocol. After correction for confounders, the change in EF was not independently predictive of the occurrence of events.

Clinical Implications

In the last decades, perfusion and function information obtained from stress/rest gated-SPECT MPI has provided powerful diagnostic and prognostic tool and has assumed a central role in the management of patients with known or suspected CAD.[1,2,4,5] Post-stress LVEF and end-systolic volumes have incremental prognostic value over perfusion data.[16] The change in LVEF has been considered as a marker of stunning and large ischemia and has providing additional diagnostic and prognostic information.[17–19]

The delay between stress tracer injection and images acquisition has been documented to influence the severity of stress induced perfusion defects.[20–22]

Moreover, LV volume and EF values were also influenced by the delay from tracer injection to images acquisition, when correlated to the amount of ischemia.[23] In the study by Mut et al in the SD protocol group the rest evaluation was performed first, thus the possible effect of a prolonged stunning also affecting rest evaluation was not an issue.[23] In conventional SD protocol, however, stress study is usually performed first, to allow for the possibility of a stress-only approach in the case of normal perfusion and function, thus requiring one tracer injection only. In our study, rest study in the SD protocol was performed on average 3 h after stress study and the possibility of a prolonged stunning in patients with severe ischemia, affecting rest LVEF, may explain the underestimation of the change in LVEF when compared to the DD protocol.[21] Our results are in agreement with those previously obtained in 1089 patients from a subgroup analysis of the J-ACCESS study, were a drop in LVEF greater than 5% did not predict events.[19] The selection of a SD or a DD protocol is related to local logistics and patients preferences; however, in terms of patients' and operators' radiation exposition, the SD protocol, requiring a 3:1 activity ratio between rest and stress studies[6] seems unfavorable compared to the DD approach.

Limitations

The analysis and interpretation of gated-SPECT images were not centralized; however, this reflects a real-world snapshot, and the same approach was used in other multi-center studies.[19,24]

Randomized clinical trials are considered the gold standard in clinical evaluations. When properly conducted, randomization ensures that groups are comparable; consequently, any difference detected is attributable to the intervention. Non-randomized data from observational studies can then be an alternative to randomized clinical trials, as they allow measuring the real-life practice and potentially producing more generalizable results. Unlike randomization, propensity matching could only remove overt (known) biases, but hidden biases cannot be excluded. As mentioned before the SD and DD protocols used different tracers which potentially could also be a confounder for the variability.

Finally, since the group of patients undergoing sestamibi SD protocol was not included in the matching procedure, we are not able to make inference on the possible lack of differences between sestamibi SD or DD protocol.

CONCLUSIONS

In patients with severe ischemia, a possible underestimation of myocardial stunning could be observed with the SD protocol, in comparison to a propensity matched group of patients undergoing the DD protocol. The stressor employed and the severity of the underlying CAD do not seem to influence these results.

After correction for confounders, post-stress LVEF and the amount of ischemia, but not the change in EF, were the scintigraphic predictors of events; SD and DD protocols come out of equal value in predicting the occurrence of clinical events.

NEW KNOWLEDGE GAINED

Post-stress left ventricular ejection fraction and the amount of ischemia, obtained either with a SD or DD gated-SPECT protocol, provide comparable prognostic information. The change in EF (stress-rest) was not independent predictors of events. The change in EF is less in severe ischemia with SD than DD protocol.

Authors Contribution

CMarcassa contributed in conception, design and analysis and interpretation of data; drafting of the manuscript; final approval of the manuscript. R. Giubbini contributed in conception, design and analysis and interpretation of data; revising the manuscript critically for important intellectual content and final approval of the manuscript. W. Acampa contributed in conception, design and interpretation of data; drafting of the manuscript; final approval of the manuscript. C. Cittanti contributed by active involvement in collecting data; revising the manuscript critically for important intellectual content. A. Gimelli contributed in conception, design and interpretation of data; drafting of the manuscript; final approval of the manuscript. G. Medolago contributed by active involvement in collection and analysis/interpretation of data. E. Milan contributed in revising the manuscript critically for important intellectual content, final approval of the manuscript. R. Sciagrà contributed in revising the manuscript critically for important intellectual content and final approval of the manuscript. O. Djepaxhija contributed by active involvement in collection and analysis of data. A. Kokomani contributed by active involvement in collection and analysis of data.

Disclosure

The authors have indicated that they have no financial conflict of interest.

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