



Effect of changes in perfusion defect size during serial stress myocardial perfusion imaging on cardiovascular outcomes in patients treated with primary percutaneous coronary intervention after myocardial infarction

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Background. We evaluated the prognostic value of changes in perfusion defect size (PDS) on serial MPS in patients treated with primary percutaneous coronary intervention (PCI) after acute myocardial infarction (AMI).

Methods. We enrolled 112 patients treated with primary PCI after AMI who underwent two stress MPS within 1 month and after 6 months. Improvement in PDS was defined as a reduction $\geq 5\%$. Remodeling was defined as an increase in left ventricular (LV) end-diastolic volume index $\geq 20\%$. Cardiac events included cardiac death, nonfatal MI, unstable angina, repeated revascularization, and heart failure.

Results. During a median follow-up of 86 months, 22 events occurred. Event rate was higher ($P < .01$) in patients with worsening of PDS compared to those with unchanged or improved PDS. Moreover, patients with remodeling had a higher ($P < .001$) event rate compared to those without. At Cox analysis, worsening of PDS and remodeling resulted independent predictors of events (both $P < .01$). Patients with both worsening of PDS and remodeling had the worst event-free survival ($P < .001$).

Conclusion. In patients treated with primary PCI after AMI, worsening of PDS and remodeling are associated to higher risk of events at long-term follow-up. Gated stress MPS improves risk stratification in these patients. (J Nucl Cardiol 2022;29:2624–32.)

Key Words: SPECT • MPI • Diagnostic and prognostic application

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Abbreviations

AMI	Acute myocardial infarction
PCI	Percutaneous coronary intervention
MPS	Single-photon emission computed tomography myocardial perfusion imaging
LV	Left ventricular
PDS	Perfusion defect size
EDV	End-diastolic volume
ESV	End-systolic volume
EF	Ejection fraction
AER	Annual event rate

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INTRODUCTION

Currently, primary percutaneous intervention (PCI) is the treatment of choice for acute myocardial infarction (AMI) to improve outcome by limiting the extent and severity of perfusion defects.¹ Nevertheless, additional myocardial damage and cardiac remodeling of the left ventricle can develop during the first months after an acute event, with a negative influence on long-term prognosis.^{2,3} Single-photon emission computed tomography myocardial perfusion imaging (MPS) has been widely used in patients treated with primary PCI, to confirm the success of revascularization and to estimate the risk of cardiac death or reinfarction.^{4,5} Serial evaluation of left ventricular (LV) myocardial perfusion and function by gated MPS has also been proposed to guide management after revascularization procedures.⁶ Prior studies found a significant correlation between perfusion parameters measured in the subacute phase after AMI and functional outcome.^{7–9} In particular, infarct size and severity, evaluated by gated MPS one week after AMI, predict cardiac remodeling during follow-up.⁹ Moreover, infarct size is independently associated with cardiac death and reinfarction beyond clinical variables during long-term follow-up.¹⁰ The variations in the extent and severity of myocardial perfusion defects and functional impairment may also have an impact in the long-term risk of AMI patients treated with primary PCI. The aim of the present study was to evaluate the prognostic value of changes in perfusion defect size (PDS) on serial MPS in patients treated with primary PCI after AMI.

METHODS

Study Population

The study population consisted of 121 patients treated with primary PCI for AMI at the University of

Naples Federico II from February 2009 to December 2011, who underwent two stress MPS within 1 month (MPS-1) and 6 months (MPS-2) after PCI. AMI was diagnosed according to American College of Cardiology/American Heart Association guidelines.¹¹ The exclusion criteria were previous MI or revascularization procedure (based on history, electrocardiogram, and echocardiographic pattern); persistence or recurrence of typical or atypical angina; repeated coronary revascularization within 6 months from MPS-2, severe ventricular arrhythmias, second- or third-degree atrioventricular block; valvular disease requiring surgery; pericarditis; severe renal dysfunction (i.e., creatinine plasma levels >2.5 mg/dl); severe concomitant noncardiac diseases, dementia, and inability to participate in a prospective study for any reason. The Ethics Committee of our Institution approved the protocol and all subject provided informed consent.

Gated SPECT

All patients underwent single-day stress/rest ^{99m}Tc sestamibi gated MPS according to the recommendations of the European Association of Nuclear Medicine.¹² Gated MPS studies were acquired using a dual-head rotating gamma camera (E.CAM, Siemens Medical Systems, Hoffman Estates, IL, USA) equipped with a low-energy, high-resolution collimator and connected with a dedicated computer system. Imaging was started 60 min after the tracer injection at rest and 45 min after pharmacological stress with dipyridamole (0.142 mg/kg per min intravenous over 4 min). The image interpretation was performed in the absence of attenuation or scatter correction. An automated software program (e-soft, 2.5, QGS/QPS, Cedars-Sinai Medical Center, Los Angeles, CA) was used to calculate end-diastolic volume (EDV), end-systolic volume (ESV), LV ejection fraction (EF), and the scores incorporating both the extent and severity of perfusion defects, using standardized segmentation of 17 myocardial regions.^{13,14} Volumetric data were corrected for body surface area and expressed as indexes (I). Perfusion defects were quantitated as % of LV myocardium and expressed as PDS (total perfusion defect), ischemia (reversible perfusion defect), and scar (fixed perfusion defect). Abnormal perfusion was defined as PDS $\geq 5\%$ LV mass.^{15,16}

Variations in perfusion pattern between MPS-1 and MPS-2 were categorized as improvement, with a decrease of $\geq 5\%$ in PDS; no change; and worsening with an increase of $\geq 5\%$ in PDS. Remodeling was defined as an increase in LVEDVI at MPS-2 $\geq 20\%$ from MPS-1.⁹

Follow-Up

Patient follow-up was prospectively obtained by use of a questionnaire that was assessed by a phone call to all patients and/or general practitioners or cardiologists and by review of hospital or physicians' records by individuals blinded to the patient's test results. The end point was the occurrence of cardiac death, nonfatal MI, unstable angina, repeated late coronary revascularization, and heart failure whichever occurred first. Cardiac death, defined as due to new AMI, ventricular arrhythmias, refractory heart failure, or cardiogenic shock, was confirmed by review of death certificate, hospital chart, or physician's records. Nonfatal MI was defined based on the criteria of typical chest pain, elevated cardiac enzyme levels, and typical alterations of the ECG. Heart failure was considered as event as worsening signs and symptoms, signifying failure of the primary therapeutic management strategy, and resulting in escalation of therapy as an outpatient or requiring hospital admission.¹⁷ Unstable angina is defined as myocardial ischemia at rest or on minimal exertion in the absence of acute cardiomyocyte injury/necrosis.¹⁸ Patients experiencing noncardiac death during follow-up were censored at the time of death. The date of the last examination or consultation was used to determine follow-up.

Statistical Analysis

Continuous variables were expressed as mean \pm standard deviation and categorical data as percentage. Differences between groups were analyzed by unpaired *t* test and χ^2 analysis as appropriate. A *P* value <0.05 was considered statistically significant. Annualized event rates (AER) expressed as % person-years were calculated as the cumulative number of events divided by person-time. Univariable and multivariable Cox regression analyses for the composite endpoint of cardiac death, nonfatal MI, unstable angina, repeated coronary revascularization, and heart failure were performed. The incremental prognostic value of clinical data and imaging findings considering variables in hierarchical order was assessed by the likelihood ratio χ^2 . Event-free survival curves were obtained by the Kaplan-Meier method and compared with the log-rank test. As the analysis focused on the prognostic value of serial changes in perfusion pattern, landmark analyses of outcomes starting at 6 months were performed. Statistical analysis was performed with STATA 15.0 for Windows (StataCorp LP, College Station, TX).

RESULTS

Follow-up was 97% complete, leaving 112 patients for the final analysis. During a median follow-up of 86 months (range 13-170), 22 events occurred in 22 patients (20% cumulative event rate, annual event rate 2.2% person-years). The events were cardiac death in 4 (18%), nonfatal MI in 6 (27%) patients, typical angina in 11 (50%) patients requiring coronary revascularization in 9 subjects, and heart failure in 1 (5%) patient. Clinical characteristics at MPS-1 in patients with and without events are presented in Table 1. Patients with events were slightly older compared to those without. Of the 9 patients with chest pain at MPS-1, 4 had ischemia and no one experienced a cardiac event during follow-up.

Imaging findings at MPS-1 and MPS-2 in the overall patient population are reported in Table 2. All perfusion defects were in the territory of the infarct-related coronary artery. In Fig. 1, MPS-1 and MPS-2 perfusion findings in patients with and without events are reported. Changes in stress and rest LVEF from MPS-1 (1 month) to MPS-2 (6 months) according to occurrence of cardiac events are depicted in Fig. 2.

Changes in PDS and LV Function According to Events

PDS improved in 35 (31%) patients, remained unchanged in 64 (57%), and worsened in 13 (12%) patients. The AER was higher (*P* $< .001$) in patients with PDS worsening compared to those with unchanged or improved PDS (Fig. 3). Cardiac remodeling was observed in 13 (12%) patients, of whom 5 (38%) showed PDS worsening. The AER was significantly higher in patients with remodeling as compared to those without (9.3% vs. 1.4%, *P* $< .001$).

Predictors of Events

The results of Cox univariable and multivariable analyses are shown in Table 3. At multivariable analysis, worsening in PDS and remodeling resulted independent predictors of events. The difference in PDS values between MPS-1 and MPS-2 was a significant predictor of outcome (hazard ratio 1.06, 95% confidence interval 1.02-1.10; *P* $< .01$). The addition of remodeling to a model including clinical variables and categories of PDS changes increased the global χ^2 from 3.68 to 45.91 (*P* $< .05$). The AER of patients with or without PDF worsening and with or without LV remodeling is reported in Figure 4. The worst outcome was observed in patients with PDS worsening and remodeling (log-rank 51, *P* for trend $<.001$) (Fig. 5). Two representative examples of patients with worsened (A)

Table 1. Clinical characteristics at MPS-1 in patients with and without events

	All patients (n = 112)	Event (n = 22)	No event (n = 90)	P value
Age (years)	55 ± 9	58 ± 8	54 ± 9	<.05
Male gender, n (%)	102 (91)	22 (100)	80 (89)	0.10
Diabetes, n (%)	21 (19)	6 (27)	15 (17)	0.25
Hypertension, n (%)	58 (52)	9 (41)	49 (54)	0.25
Dyslipidemia, n (%)	64 (57)	9 (41)	55 (61)	0.09
Smoking history, n (%)	35 (31)	6 (27)	29 (32)	0.65
Family history of CAD, n (%)	34 (30)	7 (32%)	27 (30)	0.87
Chest pain, n (%)	9 (10)	1 (5)	8 (9)	0.50
Infarct-related coronary artery, n (%)				
Left anterior descending	74 (66)	15 (68)	59 (65)	0.27
Left circumflex	18 (14)	3 (14)	15 (17)	0.63
Right coronary artery	20 (18)	4 (18)	16 (18)	0.52
Non-infarct-related coronary artery stenosis, n (%)	39 (35)	7 (32)	32 (36)	0.74

Values are means ± standard deviation or number (percentage) of patients
CAD, coronary artery disease

Table 2. Imaging findings at MPS-1 and MPS-2 in the overall patient population

	MPS-1	MPS-2	P value
PDS (%)	17 ± 12	15 ± 13	<.05
Scar (%)	14 ± 12	12 ± 13	<.05
Ischemia (%)	3 ± 4	3 ± 4	0.74
Stress LVEF (%)	47 ± 11	50 ± 11	<.01
Rest LVEF (%)	48 ± 10	50 ± 11	<.05

Values are means ± standard deviation
PDS perfusion defect size; LVEDVI left ventricular end-diastolic volume index; LVESV left ventricular end-systolic volume index; LVEF left ventricular ejection fraction

and unchanged (B) perfusion patterns are reported in Fig. 6.

DISCUSSION

In this prospective study, prognostic significance of the changes in perfusion and functional variables by gated MPS were assessed during a long-term follow-up in a cohort of patients with AMI treated with primary PCI. From our data, it emerged that worsening of the perfusion defects from MPS-1 (1 month) to MPS-2 (6 months) imaging and the presence of LV remodeling are associated with a poor prognosis. In particular, patients

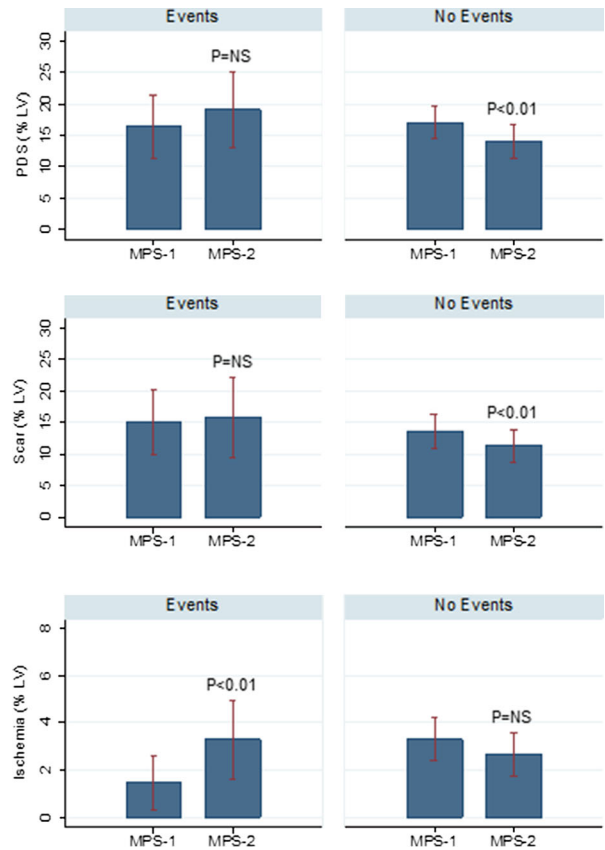


Figure 1. Changes in PDS, scar, and ischemia from MPS-1 to MPS-2 in patients with and without events.

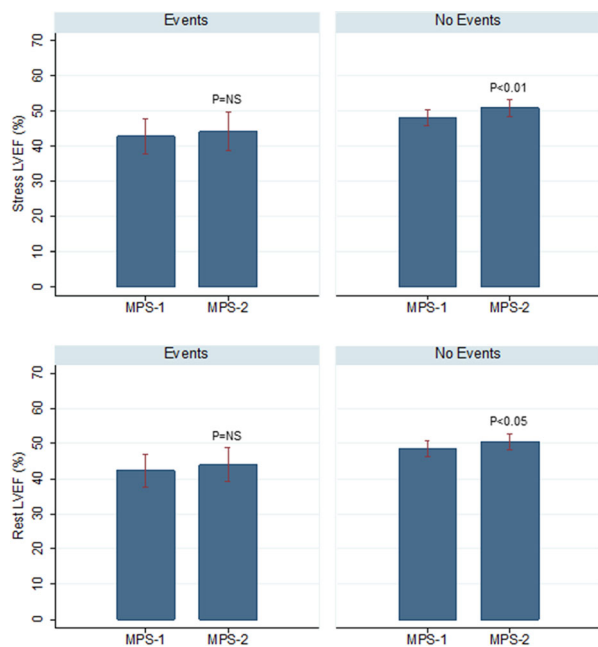


Figure 2. Changes in stress and rest LVEF from MPS-1 to MPS-2 in patients with and without events.

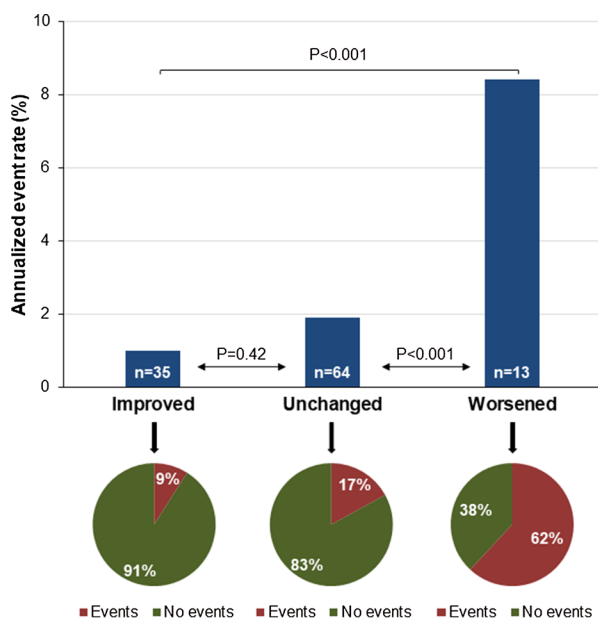


Figure 3. Annualized event rate according to changes in PDS from MPS-1 to MPS-2.

with both PDS worsening and cardiac remodeling had the worst outcome.

Primary PCI is the preferred reperfusion strategy in patients presenting with AMI. However, additional

myocardial damage and progressive enlargement or remodeling of the LV can occur during the first months after AMI, with a negative influence on long-term prognosis.^{2,3} Cardiac remodeling, defined as the progressive dilatation and change in shape, size, and function of the left ventricle, represents an important cause of heart failure in patients after AMI.¹⁹ The changes in perfusion findings, as well as of LV function over time after PCI, could give additional insight into the mechanisms of myocardial recovery used in predicting future events.²⁰

After AMI, cardiac imaging by gated MPS has been used to quantify the infarct size and severity, as well as the presence of LV functional impairment.^{21,22} Moreover, the availability of software for automated reproducible quantitative assessment made gated MPS to be particularly effective in serial evaluation⁶. From published data, it emerged a significant late reduction in infarct size in patients after AMI probably related to the vascular stunning and gradual recovery of microvascular function.^{23,24} Berti et al.⁹ confirmed that in patients submitted to successful PCI, a spontaneous reduction in infarct size occurs beyond the 1-month evaluation and it has been associated with improvement in LV function. They also found that infarct size measured in the subacute phase after AMI, but not late infarct resorption, is a strong predictor of LV remodeling.⁹ Those findings suggest that perfusion defect is strongly related to LV functional recovery. To take into account the amount of myocardial tissues subject to recovery after AMI, myocardial salvage area (defined as the difference between the initial area of myocardium at risk and the final area of necrosis) by gated MPS has been proposed⁸ and it resulted to be associated to the functional recovery 6 months after AMI. The amount of perfusion impairment has been also correlated with survival after medical therapy or PCI in patients with AMI. Stone et al.²⁵ evaluated the relationship between infarct size assessed early after PCI in ST-elevated MI and all-cause mortality, reinfarction, and hospitalization for heart failure. For this purpose, it was considered a pooled patient-level analysis from 10 randomized primary PCI trials, in a total of 2,632 patients.²⁵ A strong correlation between infarct size assessed within 1 month by either cardiac magnetic resonance or MPS imaging and all-cause mortality and hospitalization for heart failure during a short-term follow-up (1 year) was found. However, the stress parameters and functional impairments were not considered.²⁵ Smith et al.¹⁰ evaluated the long-term prognostic value of infarct size and myocardial ischemia on MPS in a large cohort of 1092 patients after PCI for ST-segment elevation MI. In patients with reduced LVEF, infarct size was independently associated with cardiac death or reinfarction,

Table 3. Univariable and multivariable Cox analysis for the composite endpoint of cardiac death, nonfatal MI, unstable angina, repeated coronary revascularization, and heart failure

	Univariable		Multivariable	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age	1.04 (0.99-1.08)	0.09		
MPS-2 imaging				
PDS	1.02 (0.99-1.06)	0.14		
Scar	1.02 (0.99-1.05)	0.20		
Ischemia	1.03 (0.94-1.13)	0.48		
PDS changes categories				
Unchanged (reference)	-	-	-	<.01
Improved	0.68 (0.19-2.47)	0.57	0.68 (0.19-2.48)	0.56
Worsened	5.75 (2.22-14.9)	<.001	4.15 (1.52-11.3)	<.01
Remodeling	6.04 (2.55-14.3)	<.001	4.43 (1.80-10.9)	<.01

PDS, perfusion defect size

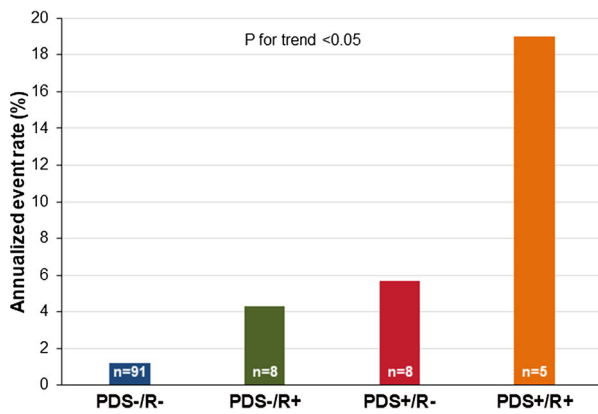


Figure 4. Annualized event rate in patients with (+) or without (–) PDS worsening and remodeling (R).

whereas myocardial ischemia was not. Conversely, in patients with LVEF >45%, only ischemia was independently associated with cardiac death or reinfarction.

In our study, we considered a smaller cohort of 112 patients evaluated with stress MPS one month and 6 months after PCI for AMI to assess the prognostic value of perfusion and functional changes in a long-term follow-up. From our data, it emerged that the worsening of PDS, but not infarct size or ischemia at 6 months (MPS-2), was predictive of prognosis. Previous studies reported that the extent and severity of perfusion defects measured within 1 week²⁶ or 6 months¹⁰ after AMI had high prognostic impact leading to an accurate risk stratification. It should be noted that differently from those previous investigations, we considered only

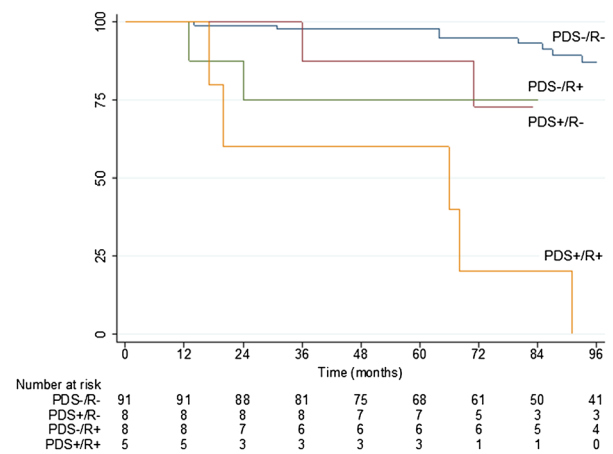


Figure 5. Event-free survival curves by Kaplan-Meier analysis in patients with (+) or without (–) PDS worsening and remodeling (R).

patients who underwent salvage reperfusion therapy within 6 hours from acute event, with a small amount of perfusion defects and relatively preserved LV function.

Our data also confirm that cardiac remodeling is a strong predictor of events.²⁷ However, despite a significant association between infarct size and cardiac remodeling has been reported,⁹ in our population, we did not identify any predictor of cardiac remodeling. This is probably due to the small number of patients (n = 13) who showed LV remodeling. Despite this, at survival analysis, the worst prognosis has been observed in patients with both perfusion worsening and

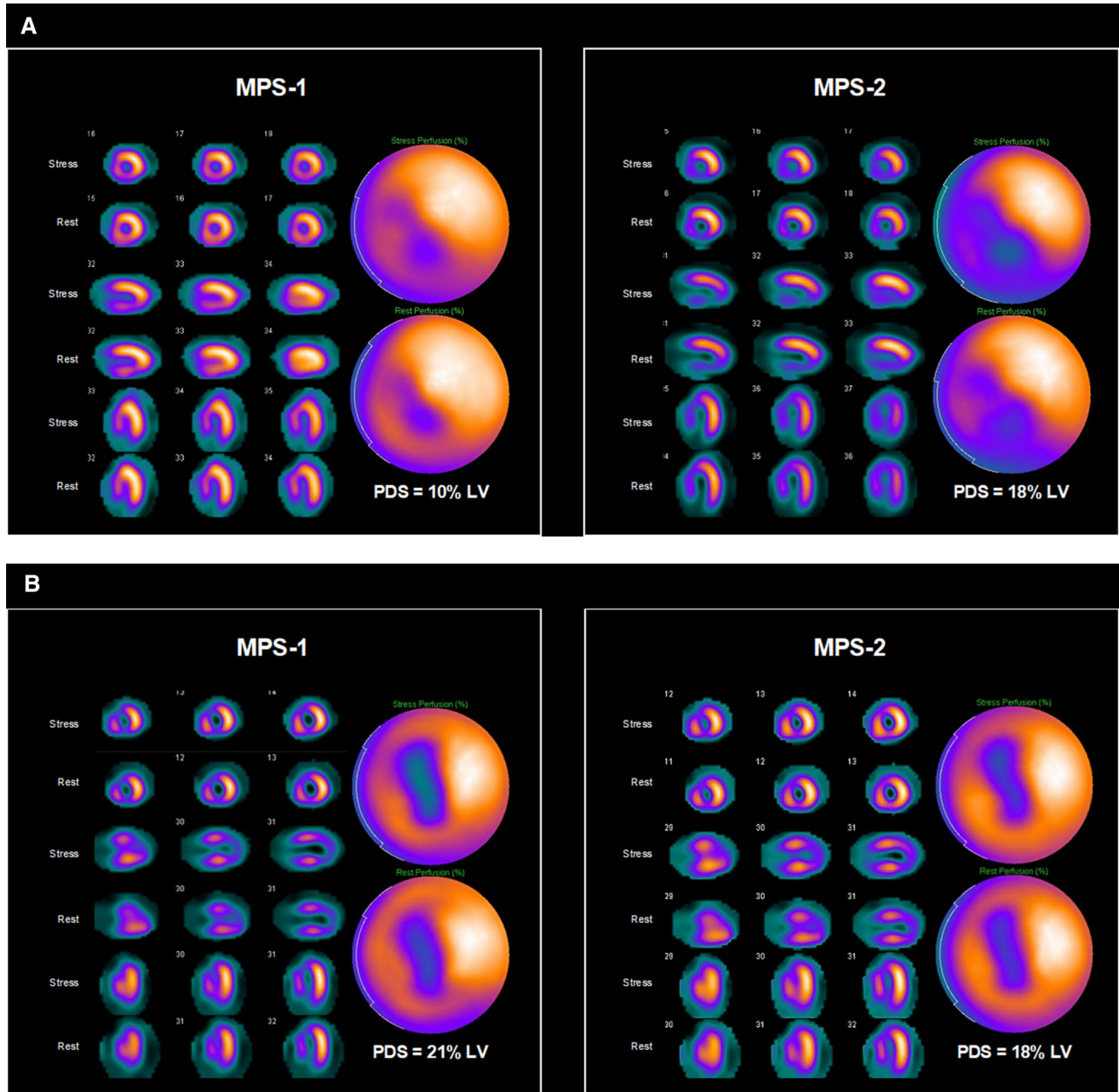


Figure 6. Changes in perfusion pattern between MPS-1 and MPS-2 in a patient with worsening of PDS who underwent a coronary revascularization procedure 24 months after MPS-2 (A) and in a patient with unchanged PDS without events at the end of follow-up (B).

remodeling, suggesting a synergic effect of perfusion and functional impairment on prognostication.

This study has some limitations that must be considered. The patient population and the number of events were relatively small and selected according to the availability of the gated MPS studies. Subjects with a history of prior MI and patients with suboptimal PCI results were not considered. Therefore, our observations might not apply to those patients. It should be also

considered that in the present study, patients were referred to stress MPS as part of a research protocol. Radionuclide imaging following PCI is not recommended in asymptomatic patients <2 years after revascularization procedures.²⁸ Despite our result may contribute to elucidate the prognostic implications of perfusion and functional changes after PCI, this method cannot be applied in clinical routine.

NEW KNOWLEDGE GAINED

This study first demonstrated that worsening of gated MPS parameters at 6 months in patients treated with primary PCI after AMI is associated to an unfavorable outcome at long-term follow-up. Serial imaging with gated MPS might be used to assess the changes in perfusion and functional parameters able to identify the patients at higher risk of cardiac events during long-term follow-up.

CONCLUSION

Patients treated with primary PCI after AMI with PDS worsening and cardiac remodeling are at higher risk of events. The identification of patients with both perfusion and functional impairment at gated MPS may have a role in risk stratification of patients after AMI in a long-term follow-up.

Disclosure

Emilia Zampella, Teresa Mannarino, Valeria Gaudieri, Adriana D'Antonio, Francesco Giallauria, Roberta Assante, Valeria Cantoni, Roberta Green, Ciro Gabriele Mainolfi, Carmela Nappi, Andrea Genova, Mario Petretta, Alberto Cuocolo, and Wanda Acampa declare that they have no financial conflict of interest.

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