Influence of Myocardial Ischemia Extent on Left Ventricular Global Longitudinal Strain in Patients After ST-Segment Elevation Myocardial Infarction

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Two-dimensional echocardiographic left ventricular (LV) global longitudinal strain (GLS) after ST-segment elevation myocardial infarction (STEMI) is moderately correlated with infarct size and reflects the residual LV systolic function. This correlation may be influenced by the presence of myocardial ischemia. The present study investigated how myocardial ischemia modulates the correlation between LV GLS and infarct size determined with single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) in patients with first STEMI treated with primary coronary intervention. A total of 1,128 patients (age 60 ± 11 years) who underwent SPECT MPI for the evaluation of infarct size and residual ischemia were evaluated. LV GLS was measured on transthoracic echocardiography. The time interval between echocardiography and SPECT MPI was 1 ± 1 month. A moderate correlation between echocardiographic LV GLS and infarct size on SPECT MPI was observed ($r = 0.58$, $p < 0.001$). This correlation was weakened by the presence or extent of ischemia; in the group of patients without ischemia, the correlation between LV GLS and infarct size on SPECT MPI was $r = 0.66$ ($p < 0.001$), whereas in patients with mild or moderate-to-severe ischemia, the correlations were $r = 0.56$ and 0.38, respectively (both $p < 0.001$). Moderate-to-severe myocardial ischemia was independently associated with more impaired LV GLS after adjusting for infarct size, age, diabetes mellitus, and hypertension (β 0.60, 95% confidence interval 013 to 1.06). In conclusion, the presence of myocardial ischemia after STEMI impacts on the correlation between echocardiographic LV GLS and infarct size measured on SPECT MPI. Residual ischemia is independently associated with more impaired LV GLS. **(Am J Cardiol 2017;119:1−6)**

Left ventricular ejection fraction (LVEF) is the most widely used parameter for risk stratification of patients with ST-segment elevation myocardial infarction (STEMI).[1] However, LV global longitudinal strain (GLS) measured with speckle tracking echocardiography may better reflect the extent of myocardial infarction and the residual LV systolic function.[2−4] A strong correlation between LV GLS and infarct size assessed with late gadolinium contrast-enhanced magnetic resonance imaging (LGE-MRI) or single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) has been shown.[5−10] However, this correlation is not straightforward because regional LV dysfunction may extend beyond the region of scar resulting in more impaired LV GLS. Factors that may negatively impact on LV GLS include burden of coronary artery disease, diabetes mellitus, age, hypertension, and associated valvular heart disease among others.[7,11−14]

In addition, the presence of myocardial ischemia may further impair LV GLS and weaken the correlation between LV GLS and infarct size. The present study evaluated the influence of myocardial ischemia on the correlation between LV GLS and infarct size in patients with STEMI who were clinically referred to SPECT MPI. Moreover, the independent association between myocardial ischemia and LV GLS was investigated.

Methods

A total of 1,224 patients with a previous first STEMI treated with primary coronary intervention at the Leiden University Medical Center (The Netherlands) from 2004 to 2010 who were clinically referred for SPECT MPI were included (to evaluate infarct size and residual ischemia).[15] The echocardiographic study closest to the date of SPECT MPI was selected to assess LV GLS.

Demographic, clinical, nuclear imaging, and echocardiographic data were prospectively entered in the

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See page 6 for disclosure information.

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departmental Cardiology Information System (EPD-Vision; Leiden University Medical Center, The Netherlands) and retrospectively analyzed. The Institutional Review Board of the Leiden University Medical Center approved the study and waived the need for written informed consent for retrospective analysis of clinically acquired data.

Echocardiographic images were obtained with the patient lying in the left lateral decubitus position. The data were acquired with commercially available ultrasound systems (Vivid 7 and E9; General Electric-Vingmed, Horten, Norway) with 3.5-MHz or M5S transducers. Two-dimensional, color, continuous, and pulsed-wave Doppler data were acquired from the parasternal (long- and short-axis) and apical (2-, 3-, and 4-chamber) views. Data were digitally stored for subsequent offline analysis with EchoPac 112.0.1 (GE Medical Systems, Horten, Norway). LVEF was calculated from the LV end-diastolic and end-systolic volumes measured from the apical 4- and 2-chamber views using the biplane Simpson method.[1] In addition, LV diastolic dysfunction was assessed measuring the peak velocity of early (*E*) and late (*A*) peak diastolic velocities from the pulsed-wave Doppler transmitral flow recordings and the deceleration time of the early filling wave. In addition, tissue Doppler imaging data were acquired to measure the mitral annulus E' diastolic tissue velocity, and the E/E' ratio was calculated as a measure of LV filling pressures. An experienced observer measured LV GLS from the apical 4-chamber, 2-chamber, and long-axis views using 2-dimensional speckle tracking analysis and blinded to the information from SPECT MPI.[4] The software calculated the LV GLS as the average of the peak systolic longitudinal strain of the 3 apical views and displayed in a 17-segment "bull's eye" plot.

SPECT MPI was performed using a 2-day stress−rest protocol starting on day 1 with a stress acquisition. The patients underwent a symptom-limited bicycle test with continuous blood pressure and 12-lead electrocardiographic recording or, when unable to exercise, a dobutamine stress test (5 to 40 μg/kg/min for 15 minutes with handgrip exercise starting at 6 minutes supplemented with atropine when necessary) or an adenosine stress test (140 μg/kg/min for 6 minutes with additional bicycle riding on individual level) according to current recommendations.[16–18] At peak exercise, after 3.5 minutes of the adenosine infusion or at peak heart rate during dobutamine, 500 MBq of technetium-99m tetrofosmin was administrated intravenously. After 30 minutes, stress images were obtained with the patient lying on a supine position. On the second day, resting images were obtained 45 minutes after intravenously administration of 500 MBq technetium-99m tetrofosmin. The images were acquired with a triple-head SPECT camera (GCA 9300/HG; Toshiba Corporation, Tokyo, Japan) or a double-head SPECT camera (7200pi; Toshiba Corporation, Tokyo, Japan). All cameras were equipped with low-energy, high-resolution collimators. A 20% window was used with a 140-keV energy peak of technetium-99m, and data were stored in a 64 × 64 matrix.

Images were processed to obtain the short-axis, vertical long-axis, and horizontal long-axis tomographic sections and polar map formats, normalized to maximal activity.[16]

Table 1
Clinical characteristics

Variable	Overall population N=1128
Age (years)	60±11
Men	858 (76%)
BMI>30kg/m^2	186 (17%)
Hypercholesterolemia*	203 (18%)
Hypertension†	381 (34%)
Current smoker	556 (49%)
Family history of CAD	499 (44%)
Diabetes mellitus	97 (9%)
LAD culprit vessel	516 (46%)
Multi-vessel CAD	591 (52%)
TIMI flow 2-3	1112 (99%)
Peak CPK level (U/L)	1531 (IQR 751-3,129)
Peak cTnT level (μg/L)	4.05 (IQR 1.6-7.9)
eGFR level (mL/min/1.73m^2)	97 (IQR 77;118)
Medications at discharge	
ACE-inhibitors/ARBs	1105 (98%)
Antiplatelet therapy	1128 (100%)
Beta-blockers	1073 (95%)
Statins	1122 (99.5%)

ACE-I = ACE-inhibitor; AT-II = angiotensin-II receptor antagonist; BMI = body mass index; CAD = coronary artery disease; CPK = creatine phosphokinase; eGFR = glomerular filtration rate estimated with the Cockroft-Gault formula; LAD = left anterior descending; TnT = troponin T; TIMI = Thrombolysis In Myocardial Infarction.

* Serum total cholesterol ≥230 mg/dl and/or serum triglycerides ≥200 mg/dl or therapeutic treatment with lipid lowering drugs.

† Defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or the use of antihypertensive medication.

The SPECT MPI data were scored semiquantitatively according to the 17-segment model.[19] Each segment was scored on a 5-point scale: 0: normal, 1: slight reduction of tracer uptake (not definitely abnormal), 2: moderate reduction of uptake (definitely abnormal), 3: severe reduction of uptake, and 4: absence of uptake.[20] The summed stress score (SSS) and summed rest score (SRS) were calculated by the summation of the segmental scores at stress and rest, respectively. The summed difference score (SDS), reflecting the stress-inducible ischemia size, was calculated by subtracting the SRS of the SSS. Afterward, the SSS and the SRS were divided into tertiles. The SDS was categorized in 3 groups: SDS 0 (no ischemia), 1 to 3 (mild−moderate ischemia), and ≥4 (severe ischemia).

Normally distributed variables are expressed as mean ± standard deviation and non-normally distributed variables as median and interquartile range. Categorical variables are presented as frequencies and percentages. The correlation between LV GLS and infarct size on SPECT MPI was evaluated with Pearson correlation. Afterward, the total population was divided into 3 groups according to the presence of no (SDS = 0), mild (SDS 1 to 3), or moderate-to-severe ischemia (SDS ≥4). Subsequently, the correlation between LV GLS and infarct size was assessed in each subgroup using Pearson correlation. The association between (mild or moderate-to-severe) ischemia and LV GLS was corrected for factors known to affect LV GLS

Table 2
Echocardiographic parameters

Echocardiography parameters	Overall population N=1128
Left ventricular end-systolic volume (mL)	58±28
Left ventricular end-diastolic volume (mL)	116±40
Left ventricular ejection fraction (%)	51±10
Left ventricular global longitudinal strain (%)	-17.4±3.9
E/A ratio	1.03±0.48
Deceleration time (ms)	244±83
E/E' ratio	13±7
Mitral regurgitation ≥ grade 2	107 (9%)

Table 3
Single-photon emission computed tomography myocardial perfusion imaging parameters

SPECT parameters	Overall population N=1128
Stress test	
Exercise	850 (75%)
Adenosine	271 (24%)
Dobutamine	7 (0.6%)
Maximal exercise (Watt)	155±43
Validity (%)	106±19
Symptoms during exercise	51 (5%)
ECG during exercise	
Positive	154 (14%)
Negative	944 (84%)
Non-diagnostic	30 (2%)
Heart rate rest (/min)	79±15
Maximum heart rate during exercise (/min)	138±29
Systolic blood pressure rest (mmHg)	145±24
Systolic blood pressure exercise (mmHg)	186±35
Diastolic blood pressure rest (mmHg)	84±13
Diastolic blood pressure exercise (mmHg)	91±17
Infarct size / summed rest score	
median	11 (IQR 4;22)
1e tertile SRS ≤ 6	404 (36%)
2e tertile SRS 7-18	371 (33%)
3e tertile SRS ≥ 19	353 (31%)
Ischemia size / summed difference score	
median	0 (IQR 0;4)
no ischemia / SDS 0	611 (54%)
mild ischemia / SDS 1-3	219 (12%)
moderate to severe ischemia / SDS ≥ 4	298 (26%)
Infarct + Ischemia size / summed stress score	
median	14 (IQR 7;24)
1e tertile SSS ≤ 9	405 (36%)
2e tertile SSS 10-20	354 (31%)
3e tertile SSS ≥ 21	369 (33%)

IQR = interquartile range; LVEF = left ventricular ejection fraction; SDS = summed difference score; SRS = summed rest score; SSS = summed stress score.

(age, hypertension, diabetes mellitus, and infarct size) using a multivariate linear regression analysis. The β coefficients and the 95% confidence interval (CI) were reported. A 2-sided p value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS software version 22.0 (SPSS IBM Corp., Armonk, New York).

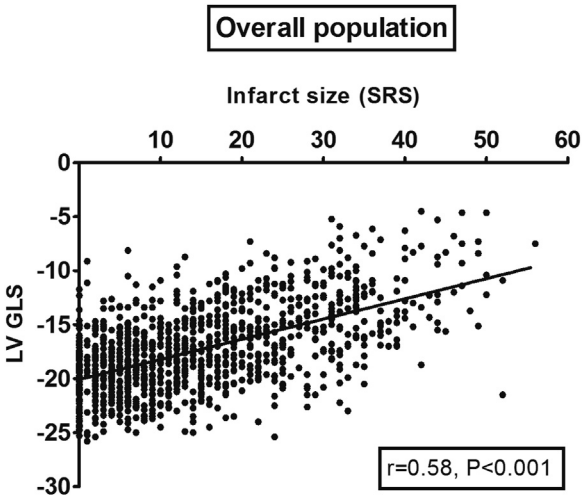


Figure 1. Pearson correlation between infarct size and LV GLS in the overall population. In the overall population, there was a moderate correlation between infarct size on SPECT MPI and LV GLS ($r = 0.58$, p <0.001).

Results

Measurement of LV GLS was not feasible in 96 patients (8%), whereas SPECT MPI examination was incomplete or uninterpretable in 19 patients (2%), leaving 1,128 patients who were considered in the analysis (Table 1). Most patients were men (76%), and the mean age was 60 ± 11 years. Left anterior descending coronary artery myocardial infarction was present in 46% of patients, and 52% had multivessel coronary artery disease.

Table 2 summarizes the echocardiographic parameters. Mean LVEF was 51 ± 10%, and mean LV GLS was −17.4 ± 3.9%. Table 3 presents the SPECT MPI results. The time elapsed between index STEMI and echocardiography was 3 ± 0.9 months, between index STEMI and SPECT MPI 3 ± 1.6 months, and between the echocardiography and the SPECT MPI 33 ± 43 days. In most patients, the stress test consisted of a symptom-limited bicycle test (75%). Fifty-one patients (4.5%) experienced cardiac symptoms during the stress test. Based on electrocardiography, 154 patients (14%) were considered as having inducible ischemia. In addition, 46% of patients showed ischemia (SDS >0), of which 298 (26%) had moderate-to-severe ischemia (SDS ≥4).

In the overall population, there was a moderate correlation between LV GLS and infarct size ($r = 0.58$, 95% CI 0.54 to 0.62, p <0.001; Figure 1). After dichotomization of the patients according to the absence or presence of ischemia, the subgroup of patients without ischemia ($r = 0.66$, 95% CI 0.61 to 0.70, p <0.001; Figure 2) showed stronger correlation between LV GLS and infarct size than in patients with mild ischemia ($r = 0.56$, 95% CI 0.45 to 0.66, p <0.001; Figure 2) and patients with moderate-to-severe ischemia ($r = 0.38$, 95% CI 0.27 to 0.47, p <0.001; Figure 2). After correcting for age, diabetes mellitus, infarct size, and hypertension, moderate-to-severe ischemia was independently associated with worse (less negative) LV GLS after STEMI (Figure 3). Figure 4 illustrates the difference in LV GLS between 2 patients with similar infarct size, but 1 patient shows ischemia, whereas the other patient does not have ischemia.

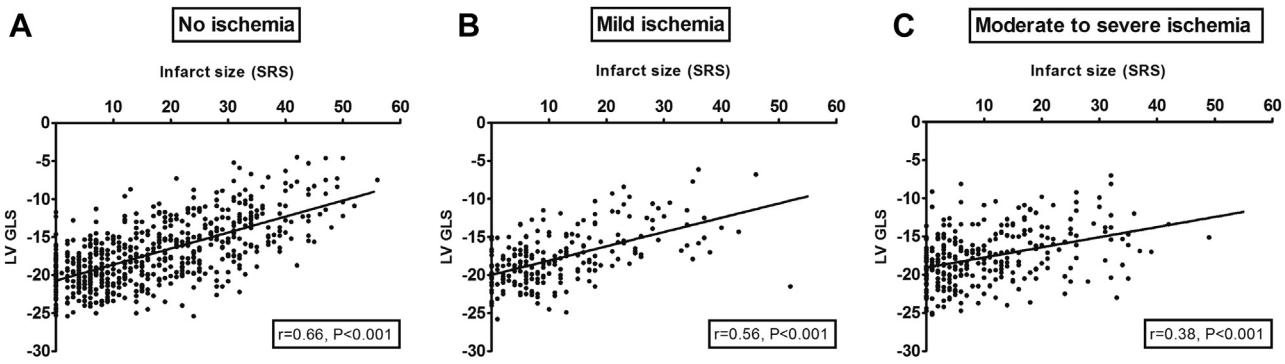
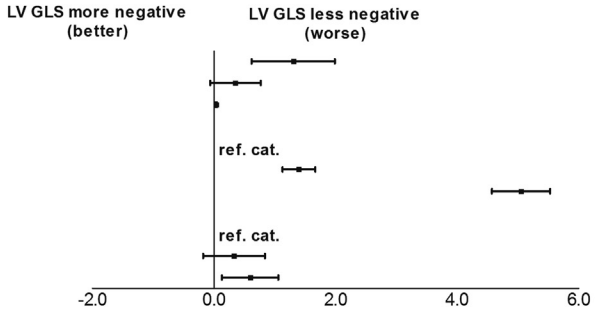


Figure 2. Pearson correlation between infarct size and LV GLS in patients without ischemia (SDS 0, *A*), mild ischemia (SDS 1 to 3, *B*), and moderate-to-severe ischemia (SDS ≥4, *C*). Patients with no ischemia (SDS 0, *A*) demonstrated a better correlation between infarct size and LV GLS ($r = 0.66$, p <0.001) in comparison to patients with mild (SDS 1 to 3, *B*; $r = 0.58$, p <0.001) and moderate-to-severe ischemia on SPECT MPI (SDS ≥4, *C*; $r = 0.38$, p <0.001).



Variables	ß (95%CI)*	P-value
Diabetes Mellitus	1.31 (0.62;1.99)	**<0.001**
Hypertension	0.35 (0.77;2.83)	0.09
Age	0.04 (0.02;0.05)	**<0.001**
Infarct size		**<0.001**
small infarct	ref. cat	
moderate infarct	1.40 (0.93;1.86)	**<0.001**
large infarct	5.05 (4.57;5.53)	**<0.001**
Ischemia size		**0.04**
no ischemia	ref. cat.	
mild ischemia	0.33 (-0.18;0.84)	0.20
Moderate to severe ischemia	0.60 (0.13;1.06)	**0.012**

Figure 3. Multivariate linear regression analysis. After correction for infarct size, diabetes mellitus, age, and hypertension, moderate-to-severe ischemia (SDS ≥4) was independently associated with worse LV GLS (β 0.60, 95% CI 0.13 to 1.06).*Increasing values represent worsening of LV function (less negative LV GLS).

Discussion

The present study demonstrated a modest correlation between LV GLS and infarct size determined on SPECT MPI in patients after STEMI. This correlation was influenced by ischemia extent: the group of patients without ischemia showed a stronger correlation between LV GLS and infarct size compared to patients with residual myocardial ischemia. The presence of myocardial ischemia was independently associated with more impaired LV GLS after adjusting for infarct size, age, diabetes mellitus, and hypertension.

Two-dimensional speckle tracking echocardiography has emerged as a quantitative method to assess LV systolic function and has shown good correlations with infarct size using LGE-MRI and SPECT MPI as reference standard (Table 4).[5–10] For example, Gjesdal et al.[6] showed that LV GLS impaired in parallel with increasing infarct size assessed with LGE-MRI 8.5 months after STEMI. The correlation between LV GLS and infarct size based on LGE-MRI was 0.84 (p <0.001). The presence of ongoing edema may overestimate the infarct size, and the presence of stunned myocardium may lead to more impaired LV GLS at early stages after STEMI, whereas at midterm follow-up, infarct size decreases and its correlation with LV GLS may change.[21] The present study is the largest so far comparing LV GLS and infarct size based on SPECT MPI and provides further insight by evaluating the influence of residual ischemia on this correlation. The presence of residual myocardial ischemia or development of new coronary lesions that cause ischemia is an important question during follow-up of survivors after STEMI. In the present study, the correlation between infarct size assessed with SPECT MPI and LV GLS was in line with previous studies (Table 4).[5–10] Importantly, infarct size was assessed at 3 months after STEMI, and in addition, the presence of myocardial ischemia was assessed, allowing to investigate whether this correlation may differ between patients with and without ischemia.

In patients with an acute infarction, the follow-up may be complicated by the presence of stress-induced ischemia which is associated with a twofold to fourfold increase in cardiac events compared to those without ischemia.[22] In the present study, 46% of the population had ischemia on SPECT MPI of which 26% were moderate-to-severe ischemia (SDS ≥4). Repetitive episodes of ischemia might result in LV dysfunction (chronically stunned myocardium).[23] Biering−Sørensen et al. demonstrated in 293 patients with clinically suspected coronary artery disease and preserved LVEF that patients with significant coronary artery disease (area stenosis ≥70% in ≥1 vessel on coronary angiography) had more impaired LV GLS compared to patients without significant coronary artery disease (−17.1 ± 2.5% vs −18.8 ± 2.6%, p <0.001).[24] LV GLS remained an independent associate of coronary artery disease after multivariate adjustment for baseline characteristics, exercise test, and conventional echocardiography (odds ratio 1.25; p = 0.016 per 1% decrease). In post-STEMI patients, the

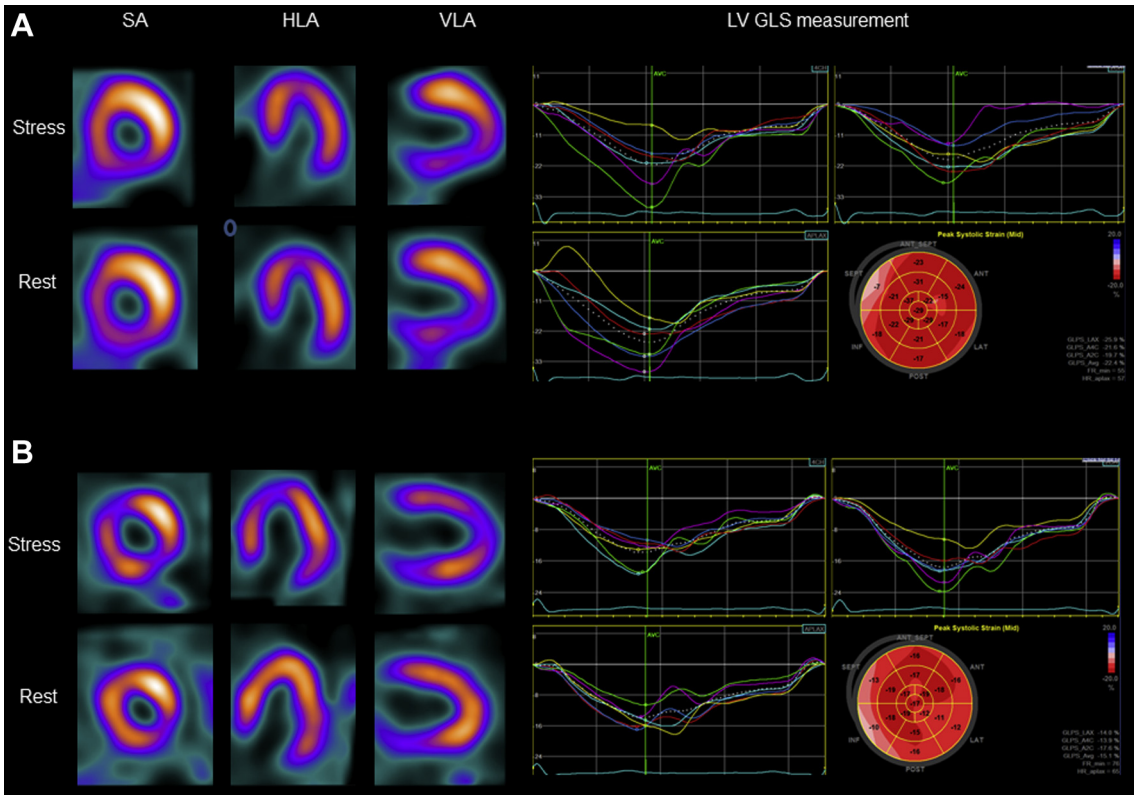


Figure 4. Left ventricular global longitudinal strain according to the presence of ischemia. *(A)* The example of a patient without ischemia on SPECT MPI with a value of LV GLS of −22.4%. *(B)* The example of a patient with ischemia and a value of LV GLS on echocardiography of −15.1%. Despite showing similar infarct size (SRS = 22), the presence of ischemia is associated with impaired LV GLS at rest. HLA = horizontal long axis; SA = short axis; VLA = vertical long axis.

Table 4
Studies evaluating the correlation between left ventricular global longitudinal strain and infarct size in post-ST-segment elevation myocardial infarction patients. Only studies with at least 25 patients were considered

	Zhu et al.[5]	Sjoli et al.[9]	Gjesdal et al.[6]	Bière et al.[8]	Wang et al.[10]	Munk et al.[7]
No. Patients	26	39	40	41	57	227
Characteristics						
Age (years)	56±11	62±9	58±10	57±12	64±13	62±11
Hypertension	-	33%	-	16%	-	33%
Diabetes Mellitus	-	8%	-	8%	-	8%
Echocardiography						
time post-STEMI	4 days	10±5 days	8.5±5.4 months	3.9±1.2 days	3-6 months	1 and 30 days
2D/3D	3D	2D	2D	2D	3D	2D
Technique for determination of infarct size	LGE-MRI	LGE-MRI	LGE-MRI	LGE-MRI	^{99}Tc-sestamibi SPECT	^{99}Tc-sestamibi SPECT
Time post-STEMI	4 days	6-23 months	8.5±5.4 months	90 days	3-6 months	30 days
Mean LV GLS (%)	<10% MIS: -16.6±2.79 10-30% MIS:-13.7±2.9 >30% MIS: -10.3±2.4	-15.6±4.6 (acute phase) -16.4±2.7 (after PCI)	<30g: -17.9±1.7 30-50g: -15.3±1.9 ≥50g: -11.2±3.2	-13.9±3.4	<30% MIS: -16.4±2.9 ≥30% MIS: -10.7±4.3	-14.8±4.1 (day 1) -16.8±3.4 (day 30)
Correlation of LV GLS and infarct size	r=0.86, P<0.01	r=0.76, P<0.0001	r=0.84, p<0.001	r=0.60, P<0.001	r=0.79, P<0.001	r=0.61,P<0.0001 (day 1) r=0.66,P<0.0001 (day 30)

2D/3D = 2-dimensional/3-dimensional; LV GLS = left ventricular global longitudinal strain; MIS = myocardial infarct size; No = number; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

assessment of myocardial ischemia may be challenged by the presence of preexistent wall motion abnormalities.[25] LV segments with impaired longitudinal strain due to the presence of scar may influence the function of surrounding segments resulting in reduced function or hyperkinesia in the remote segments. Accordingly, the correlation between LV GLS and infarct size assessed with SPECT MPI may not be straight forward, particularly, if residual ischemia of the remote and peripheral areas of the myocardial infarction is present.

Some limitations should be acknowledged. First, this was a single-center, retrospective, observational evaluation. Second, infarct size was assessed with SPECT MPI which has less spatial resolution than LGE-MRI.[25]

Disclosures

Dr. Delgado received speaker fees from Abbott Vascular. The other authors have no conflicts of interest to declare.

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