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Regional cardiac dysfunction and outcome in patients with left ventricular dysfunction, heart failure, or both after myocardial infarction

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Aims Global measures of left ventricular (LV) function, in particular LV ejection fraction (LVEF) and global myocardial strain measures, are powerful predictors of outcomes in patients with LV dysfunction, heart failure, or both. However, less is known about the relationship between regional myocardial function, especially that assessed by strain echocardiography and clinical prognosis.

Methods and results We studied 248 patients with LV dysfunction, heart failure, or both 5 days after first myocardial infarction (MI) from the VALIANT study. We assessed peak longitudinal strain (LS) via B-mode speckle tracking in 12 segments from the apical 4- and 2-chamber views and visually assessed LV wall motion score (WMS). We related these measures of regional myocardial function to each other and to clinical outcomes over 20-month follow-up. Normal reference values for segmental LS were derived from 50 healthy controls. Regional LS (-7.7%, Q_1: -11.2%, Q_3: -4.9%) was worse in segments with abnormal WMS, although was significantly impaired even in segments scored as normokinetic compared with normal controls ($-10.4 \pm 5.2\%$ vs. $-20.0 \pm 7.6\%$, $P < 0.001$). In multivariable Cox proportional hazards models, each additional abnormal LS segment was associated with an increased risk of all-cause mortality (hazard ratio: 1.42, 95% confidence interval: 1.06–1.90, $P = 0.02$) even after adjustment for clinical covariates, including LVEF, LV end-systolic volume, and number of abnormal segments by WMS.

Conclusion In patients with LV dysfunction, heart failure, or both after MI, regional LS is significantly depressed even in segments with normal WMS, and this measure was related to adverse outcome.

Keywords Regional cardiac dysfunction • Cardiovascular outcomes • Left ventricular dysfunction • Heart failure • Myocardial infarction

Introduction

Global measures of left ventricular (LV) function, in particular LV ejection fraction (LVEF), are powerful predictors of outcomes in post-myocardial infarction (MI) patients with LV dysfunction, heart failure, or both.[1–5] Wall motion score (WMS) index, a measure that is sensitive to regional LV function, has been demonstrated to be a strong predictor of adverse events after MI.[6–8] The number of affected segments, defined by worse WMS, has been shown to have better prognostic value than LVEF in MI patients with LV dysfunction, heart failure, or both.[9]

Myocardial deformation imaging utilizing speckle-tracking echocardiography enables quantification of regional myocardial function and evaluation of LV longitudinal motion. Recent studies have shown that regional longitudinal strain (LS), measured by speckle tracking, is associated with regional cardiac function recovery[10]

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and in-hospital outcomes in patients after acute MI.[11] However, less is known about the relationship between regional cardiac function and long-term clinical outcomes in MI patients. In the present study, we sought to describe regional cardiac function using both WMS and LS, which was derived from two-dimensional (2D) speckle-tracking echocardiography, and to evaluate the prognostic value of regional cardiac function on clinical outcomes in post-MI patients enrolled in the Valsartan in Acute Myocardial Infarction Trial (VALIANT) echocardiography study over 20-month follow-up.

Methods

Patient population

Among all the 14 703 VALIANT patients with MI, 610 underwent 2D echocardiography between 12 h and 10 days and were recruited into the VALIANT echocardiography substudy. All 610 patients had LV dysfunction (LVEF $<35\%$ on echocardiography or ventriculography or LVEF $<40\%$ on radionuclide imaging), clinical evidence of heart failure at the time of presentation, or both.[4,12] For this analysis, we included only patients with first MI. A scoring system (1, optimal to 3, unacceptable) was set up to select good-quality images for speckle-tracking analysis by two experienced echocardiographers. Images with at least one segment with a score of 3 were eliminated for further analysis. After review of the baseline images by two physicians blinded to outcomes, 380 patients with apical 2- and 4-chamber view images were assessed for endocardial border definition,[13] 248 first MI patients with qualified images were included in the present study. Fifty age- and gender-matched healthy controls from Brigham and Women's Hospital's outpatient department with no evidence of cardiovascular disease or abnormalities on echocardiography served as controls.

The study complies with the Declaration of Helsinki. Ethics committee at each participating site approved the research protocol. Informed consent has been obtained from the subjects.[12]

Echocardiographic analysis

Videotape echocardiographic images were converted into DICOM digital images and analysed by Cardiovascular Imaging Core Lab at Brigham and Women's Hospital as previously described and validated.[14] Traditional echocardiographic parameters, such as LV end-systolic volume, LVEF, and LV mass index, were obtained from 2D, M-mode, and Doppler images from three separate cardiac circles as previously described.[4,9,13,15] Infarct segment length was assessed by manual measurement of the infarct perimeter, defined as a severely hypokinetic, akinetic, or dyskinetic segment, and the average short-axis and apical infarct perimeter lengths were summed. The entire cavity perimeter length was measured in the apical and short-axis views, and the infarct segment length was expressed as a percentage of the total perimeter.[4]

Longitudinal strain information was obtained from DICOM images that were analysed by the offline pixel-tracking software (Velocity Vector Imaging (VVI), Siemens, Inc., Mountain View, CA, USA) at a frame rate of 30 frames/s. This previously validated software allows for precise tracking of myocardial motion with angle-independent 2D velocity and strain measures.[16] Reproducibility of these measures has also been reported by our group.[14,16] Longitudinal strain for all 12 regions from both 2- and 4-chamber views was derived, with greater myocardial shortening shown as a more negative LS value (*Figure 1*). Abnormal strain segments were decided by the normal controls. Abnormal LS segments were defined as those with strain value higher than the 95% percentile of corresponding normal control segments. Segmental cut-off values for each LV wall were shown as following (base to apex, in percentile). Inferior wall: -10.4, -11.1, and -13.7; anterior wall: -17.8, -14.4, and -6.9; septal wall: -7.8, -12.5, and -16.1; lateral wall: -14.2, -10.4, and -9.0. A segment with LS less negative than the cut-off value would be defined as an abnormal segment.

Wall motion score of the 12 segments was evaluated by a single experienced physician, who was blind to the LVEF, infarction site information, and outcomes, according to the American Society of Echocardiography guidelines.[17] Each segment was then assigned a score (1 = normokinetic, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic) according to the wall motion.[9]

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median (interquartile range), for skewed variables. Categorical variables were presented as counts and percents. One-way ANOVA

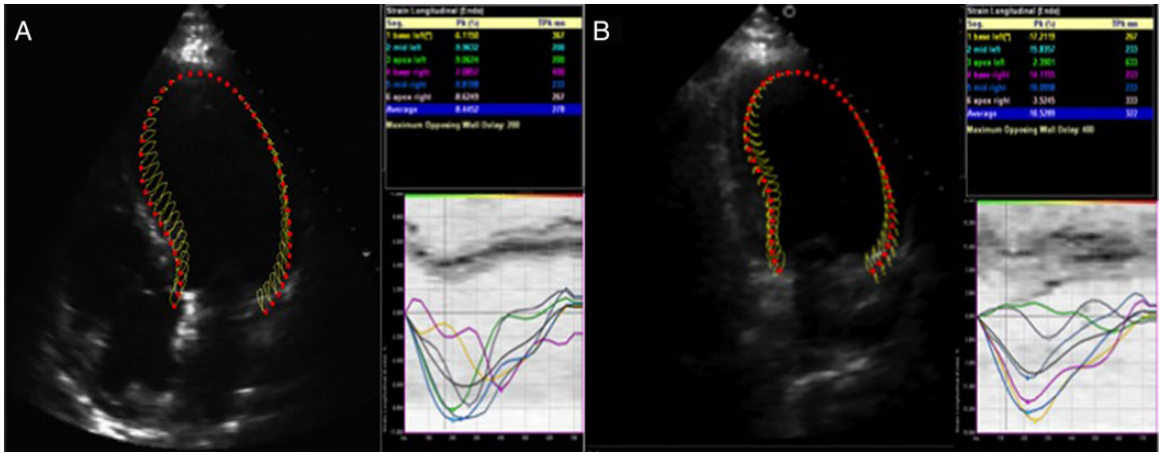

Figure 1 Apical 4-chamber (*A*) and 2-chamber (*B*) view of regional longitudinal strain in post-myocardial infarction patients.

was used to compare the five groups (control, normokinetic, hypokinetic, akinetic, and dyskinetic). Multivariable Cox proportional hazards models were used to detect the independent value of number of segments with abnormal LS on prediction of clinical outcomes (all-cause mortality, death, or hospitalization for heart failure). *C* statistics were calculated to assess the discriminatory ability of each model with respect to clinical outcomes. Variables in the adjusted model referred to those 10 previously identified predictors of mortality from the overall VALIANT study using stepwise elimination and backward selection of a 70-covariate model [age, history of diabetes mellitus, history of heart failure, history of angina, history of chronic obstructive pulmonary disease (COPD), history of atrial fibrillation, percutaneous trasluminal coronary angioplasty after MI, Killip class, estimated glomerular filtration rate (eGFR), and LVEF], as well as end-systolic volume, infarct length, and number of abnormal WMS segments as well.[4] Owing to the potential for over-fitting in the adjusted models, *C* statistics were estimated and compared using optimism-corrected bootstrap validation. $P < 0.05$ (two-tailed) was considered significant. Statistical analyses were performed with STATA, version 12.0 (Stata-Corp., College Station, TX, USA).

Results

Baseline characteristics

Among all the 14 703 patients of VALIANT study, baseline characteristics of patients included in the present study ($n = 248$) were similar with respect to gender, race, history of diabetes, type of infarction, Killip class, heart rate, eGFR, and medication at randomization, although were slightly younger (62 ± 13 vs. 65 ± 12 years, $P < 0.01$), less likely to have history of hypertension (47.6 vs. 55.4%, $P = 0.01$) and inferior MI (27.9 vs. 34.5%, $P = 0.03$), compared with patients who were not included in the present study.

Among patients stratified by number of abnormal LS segments, gender, race, body mass index (BMI), history of heart failure, diabetes, left bundle branch block (LBBB), and infarction type were comparable (*Table 1*). Patients with a greater number of abnormal LS segments were older, more likely to have hypertension, anterior MI, higher heart rate, higher end-diastolic and -systolic volume index, higher left atrial volume index, lower deceleration time, and LVEF. In addition, patients with a greater number of abnormal regional LS segments had more depressed WMS index and global LS (*Table 1*).

Regional longitudinal strain

Of all the 248 first MI patients, the global LS was -7.7% (Q_1: -11.2%, Q_3: -4.9%), the median number of abnormal LS segments was 10, more than 50% of patients had 10 or more abnormal LS segments. The distribution of number of abnormal LS segments and number of abnormal WMS segments is shown in *Figure 2*. Patients with a greater number of abnormal WMS segments also had a greater number of abnormal LS segments (*Table 2*). Regional LS was worse in segments with worse WMS ($P < 0.001$) (*Figure 3*). However, even in segments scored as normokinetic WMS, regional LS was significantly reduced compared with healthy controls ($-10.4 \pm 5.2\%$ vs. $-20.0 \pm 7.6\%$, $P < 0.001$) (*Figure 3*).

In multivariable Cox proportional hazards models, the number of segments with abnormal LS was significantly associated with all-cause mortality [hazard ratio (HR): 1.42, 95% confidence interval (CI): 1.06–1.90, $P = 0.02$] and death or hospitalization for heart failure (HR: 1.27, 95% CI: 1.07–1.51, $P < 0.01$) even after adjustment for clinical covariates, including LVEF, LV end-systolic volume, infarct length, and the number of abnormal segments by WMS. The number of abnormal LS segments was a better predictor of all-cause mortality or the combined endpoint of death or heart failure hospitalization than number of abnormal WMS segments (*Table 3*).

Discussion

In the present study, we examined regional cardiac function using 2D speckle-tracking echocardiography and evaluated the prognostic value of regional cardiac function on clinical outcomes in heart failure patients after first MI. Our data show that even in segments with normal WMS, LS is far more depressed than in healthy controls. Moreover, the number of abnormal LS segments was better than the number of abnormal WMS segments in predicting clinical outcomes in first MI patients.

Previous regional cardiac function studies have shown that WMS and LS are reduced in ischaemic regions.[18,19] In the present study, we found that segments with more restricted wall motion had more depressed LS, which is in accordance with previous findings.[18,19] In this study, we compared regional cardiac LS in segments with normal wall motion in heart failure patients after MI and that in segments of healthy controls. In post-MI patients with normal wall motion, regional LS was also largely depressed compared with healthy controls, suggesting that regional myocardial strain was abnormal even when wall motion excursion was relatively normal. While we cannot rule out the possibility that this finding is secondary to intrinsic abnormalities of myocardial function in these segments, it is more likely that strain is reduced in these normokinetic segments because of the increased load imposed by the increased wall stress in the recently infarcted ventricle. While compensatory increase in shortening of control segments has been observed in the setting of experimental MI as the consequence of regional use of the Frank–Starling mechanism,[20] our findings of reduced LS in non-infarcted segments need to be viewed in the context of an elderly population with existing comorbid disease, including diabetes, hypertension, and prior heart failure, in which myocardial function could be expected to be worse, even in non-infarcted segments, than that in health control subjects.

Previous studies have shown that regional LS provides accurate and reproducible measures of regional LV function,[21,22] although has been mostly used as an indicator of cardiovascular disease progression[23] or to assess therapeutic effectiveness.[10,24] While global LS has been shown to be a good predictor of outcome in a variety of clinical settings,[22,25,26] the predictive value of regional LS has not previously been assessed. We found that the number of abnormal LS segments was an independent predictor of both all-cause mortality and death or hospitalization for heart failure, even after adjustment for LVEF, LV end-systolic volume, and infarct segment length, and that the number of abnormal LS segments was better than the number of abnormal WMS segments, another indicator for regional cardiac dysfunction, in predicting clinical outcomes as

Table 1 Baseline characteristics of patients stratified by number of abnormal longitudinal strain segments

Variables	Tertiles of number of abnormal longitudinal strain segments			P
	<9 (*n* = 76)	9–10 (*n* = 75)	11–12 (*n* = 97)	
Age, years	59 ± 13	61 ± 12	64 ± 13	0.03
Men, *n* (%)	57 (75.0)	51 (68.0)	68 (70.1)	0.62
Race				0.75
White, *n* (%)	71 (93.4)	70 (93.3)	88 (90.7)	
Non-white, *n* (%)	5 (6.6)	5 (6.7)	9 (9.3)	
BMI (kg/m^2)	26.8 ± 4.5	27.2 ± 4.9	27.2 ± 4.1	0.76
Previous CHF, *n* (%)	6 (7.9)	8 (10.7)	14 (14.4)	0.39
Diabetes, *n* (%)	9 (11.8)	15 (20.0)	26 (26.8)	0.05
Hypertension, *n* (%)	31 (40.8)	30 (40.0)	57 (58.8)	0.02
Anterior wall infarction, *n* (%)	37 (48.7)	50 (66.7)	68 (70.1)	0.01
Type of infarction, *n* (%)				0.88
Q-wave	52 (68.4)	54 (72.0)	67 (69.1)	
Non-Q-wave	24 (31.6)	21 (28.0)	30 (30.9)	
Killip class >1	60 (79.0)	51 (68.0)	68 (70.1)	0.27
Heart rate (b.p.m.)	74 ± 12	76 ± 10	81 ± 15	<0.001
Blood pressure (mmHg)				
Systolic	118 ± 15	118 ± 13	120 ± 14	0.68
Diastolic	68 ± 11	69 ± 11	73 ± 11	0.01
LBBB, *n* (%)	5 (6.6)	3 (4.0)	5 (5.2)	0.78
eGFR (mL/min/1.73 m^2)	77 ± 20	70 ± 20	71 ± 21	0.09
Time to randomization, days	4.1 ± 2.1	5.0 ± 2.4	5.1 ± 2.6	0.02
Medication at randomization, *n* (%)				
ACE inhibitor/ARB	31 (40.8)	40 (53.3)	44 (45.4)	0.29
Beta-blocker	55 (72.4)	66 (88.0)	66 (68.0)	0.01
Statin	38 (50.0)	21 (28.0)	30 (30.9)	0.01
Digoxin	4 (5.3)	10 (13.3)	19 (19.6)	0.02
Aspirin	74 (97.4)	65 (86.7)	88 (90.7)	0.06
Primary PCI	16 (21.1)	15 (20.0)	21 (21.7)	0.97
Echocardiographic measurements				
LVEDV indexed, ml/m^2	55.4 ± 9.9	59.1 ± 12.8	65.0 ± 12.4	<0.001
LVESV indexed (mL/m^2)	32.2 ± 6.5	35.3 ± 9.1	40.8 ± 9.4	<0.001
LVEF (%)	42.2 ± 4.7	40.9 ± 4.3	37.5 ± 5.8	<0.001
LVMI (g/m^2)	91.3 ± 24.5	93.4 ± 27.1	104.7 ± 27.2	<0.01
Infarct length (%)	17.7 ± 4.3	20.3 ± 5.1	22.0 ± 5.8	<0.01
LAV indexed (mL/m^2)	21.4 ± 7.1	23.13 ± 8.4	25.7 ± 9.4	0.01
MR jet area/LA area (%)	5.6 ± 7.5	7.3 ± 7.7	7.8 ± 7.4	0.21
Wall motion score index	1.6 ± 0.3	1.8 ± 0.3	2.0 ± 0.3	<0.001
Global longitudinal strain (%)	−11.5 ± 1.8	−8.5 ± 1.4	−6.1 ± 1.5	<0.001

all-cause mortality and death or hospitalization for heart failure. Wall motion scoring relies on subjective visual assessment of wall motion excursion and thickening. Computer-based speckle tracking is likely to be more robust than visual methods. Moreover, LS may be more sensitive to abnormalities of longitudinal function that might be impaired earliest in the course of myocardial disease, as this measure primarily reflects the function of subendocardial bands. Regional strain may thus represent a robust and powerful index of myocardial function, especially in the assessment of diseases that affect the heart regionally or in the assessment of therapies that might affect myocardial function in a regional manner. The number of abnormal LS segments was a significant predictor when added to the adjusted model, but the overall model discrimination ability, as measured by the *C* statistic, improved numerically, but not significantly. This may be due to the relatively small number of events in the echo substudy.

Some limitations of this analysis should be noted. We were able to perform these analyses only in a relatively small subset ($n = 248$)

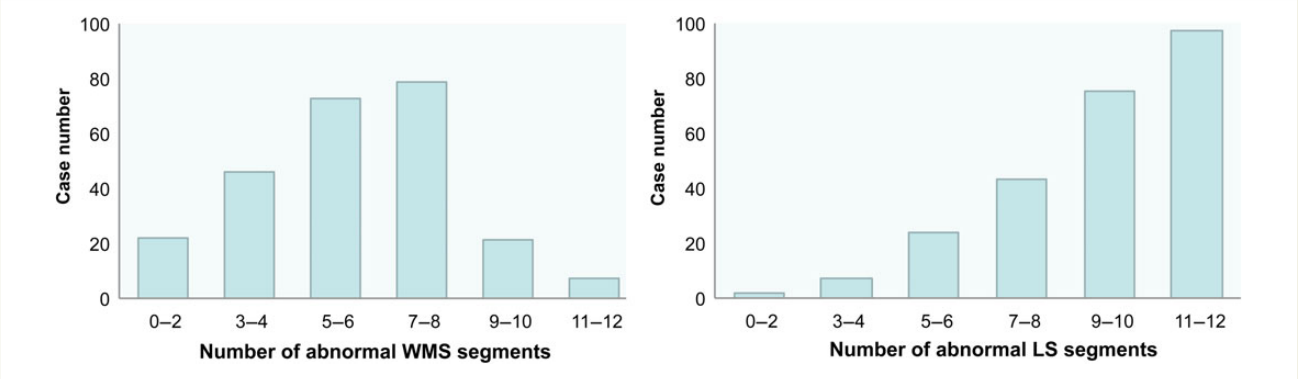

Figure 2 Case distribution by number of abnormal wall motion score and longitudinal strain segments.

Table 2 Distribution of number of abnormal segments by both wall motion score and longitudinal strain

Number of abnormal LS segments	Number of abnormal WMS segments					
	0–2	3–4	5–6	7–8	9–10	11–12
0–2	1	1	0	0	0	0
3–4	2	4	0	1	0	0
5–6	7	7	6	4	0	0
7–8	3	17	15	8	0	0
9–10	6	14	27	25	2	1
11–12	3	3	25	41	19	6

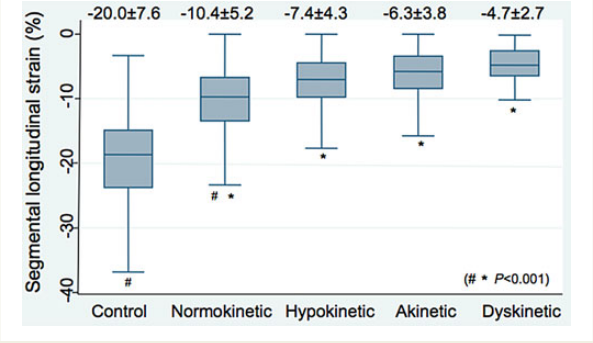

Figure 3 Segmental wall motion score and segmental longitudinal strain from healthy control and post-myocardial infarction patients.

of the VALIANT population. Nevertheless, the baseline characteristics were similar between the therefore excluded and those included patients.[13] Out-of-plane motion, lateral resolution, reverberations, and image dropouts may all affect the strain measurements, though B-mode-based speckle tracking have been shown to be more robust than Doppler-based techniques in strain evaluation.[14] While Videotape-based images have significant disadvantages compared with digitally acquired studies because of the loss of image quality and lower frame rate, we and others have previously shown that strain measures from videotape can be comparable with digital images in subjects with good-quality video-based images,[13,14,27] and we have previously shown that global strain measures derived in this manner were more predictive of outcome than conventional echocardiography measures. While VALIANT was performed in an era with less satisfactory imaging techniques and did not mandate the use of second harmonic imaging, we rigorously assessed image quality and excluded those cases without sufficient speckle-tracking results based on analysable individual segments numbers, which resulted in higher images quality for the remaining analysable cases.[13] Jet area/left atrial area ratio was employed as the indicator of mitral regurgitation. While this is not the most robust method to assess mitral regurgitation, VALIANT was a multicentre trial and more accurate methods, including proximal isovelocity surface area or vena contracta, were not obtained. Nevertheless, this measure of mitral regurgitation has been related to outcomes in this cohort.[28]

In the present study, we observed a gradient of segmental LS from the basal to apical segment at each left ventricle wall. In the lateral and anterior segments, the LS values get more negative from apex to base. In the septal and inferior segments, the LS values get more negative from base to apex. This pattern was consistent in our normal controls and in the VALIANT MI patients. These specific patterns may be somewhat different from deformation data utilizing other vendors, particularly the GE system (EchoPac Vingmed), which tends to report more negative left ventricle apical LS values when compared with middle or basal segments. This difference may be due to different post-processing algorithms to define the direction of contraction and relative motion of regional myocardial function by different observation points used.[29–31] The algorithm based on VVI that we employed, which is identical to that used by TomTec (Munich, Germany), utilizes a single fixed reference point to define all other regional myocardial strains,[30] which is different from the GE algorithm that is based on an echo beam axis-based calculation, which may account for some differences in the strain patterns observed by various vendors. The specific pattern of a gradient from base to apex is consistent with other reports using VVI or TomTec software,[32–35] has been validated, and is internally consistent.

Table 3 Prognostic value of number of abnormal longitudinal strain segments and number of abnormal wall motion score segments on clinical outcomes

	All-cause mortality			Death or hospitalization for heart failure		
	Hazard ratio (95% CI)	*C* statistic value (95% CI)	*P*	Hazard ratio (95% CI)	*C* statistic value (95% CI)	*P*
Univariable						
Number of abnormal LS segments	1.34 (1.09–1.65)	0.65 (0.57–0.74)		1.21 (1.06–1.41)	0.61 (0.54–0.69)	
Number of abnormal WMS segments	1.21 (1.05–1.41)	0.59 (0.49–0.70)		1.24 (1.10–1.39)	0.63 (0.55–0.70)	
Multivariable						
Adjusted variables[a]		0.74 (0.66–0.83)			0.80 (0.74–0.86)	
Multivariable[a] with number of abnormal LS segments	1.39 (1.05–1.83)	0.76 (0.68–0.84)	0.35	1.27 (1.08–1.50)	0.81 (0.76–0.87)	0.16
Multivariable[a] with number of abnormal WMS segments	1.02 (0.83–1.26)	0.73 (0.65–0.81)	–	1.07 (0.90–1.26)	0.79 (0.73–0.86)	–
Multivariable[a] with both						
Number of abnormal LS segments	1.42 (1.06–1.90)	0.75 (0.67–0.83)	0.51	1.27 (1.07–1.51)	0.81 (0.75–0.87)	0.30
Number of abnormal WMS segments	0.94 (0.76–1.17)			0.99 (0.84–1.18)		

[a]Adjusted for age, history of diabetes mellitus, history of heart failure, history of angina, history of COPD, history of atrial fibrillation, percutaneous trasluminal coronary angioplasty after MI, Killip class, eGFR, LVEF, LV end-systolic volume, and infarct length in percent.

Conclusion

In patients with LV dysfunction, heart failure, or both after first MI, regional LS was significantly depressed even in segments with normal WMS. The number of abnormal LS segments was predictive of all-cause mortality and death or hospitalization for heart failure, independent of LVEF, LV end-systolic volume, and infarct length. Moreover, this measure performed better than the number of abnormal WMS segments, another indicator for regional cardiac dysfunction, in predicting clinical outcomes. These findings suggest that strain-based measures of regional myocardial function may play a role in prognostic assessment of myocardial diseases.

Authors' contributions

N.W., C.-L.H., S.-H.S., B.C., H.S., J.J.T., A.S., and S.D.S.: performed statistical analysis. M.A.P. and S.D.S.: handled funding and supervision. N.W., C.-L.H., S.-H.S., and J.J.T.: acquired the data. S.D.S.: conceived and designed the research. S.D.S. and N.W.: drafted the manuscript. S.D.S., N.W., C.-L.H., L.K., J.J.V.M., and M.A.P.: made critical revision of the manuscript for key intellectual content.

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