Relationship between Left Ventricular Longitudinal Deformation and Clinical Heart Failure during Admission for Acute Myocardial Infarction: A Two-Dimensional Speckle-Tracking Study

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Background: Heart failure (HF) complicating acute myocardial infarction (MI) is an ominous prognostic sign frequently caused by left ventricular (LV) systolic dysfunction. However, many patients develop HF despite preserved LV ejection fractions. The aim of this study was to test the hypothesis that LV longitudinal function is a stronger marker of in-hospital HF than traditional echocardiographic indices.

Methods: A total of 548 patients with acute MIs were evaluated (mean age, 63.2 ± 11.7 years; 71.6% men). Within 48 hours of admission, comprehensive echocardiography with assessment of global longitudinal strain (GLS) was performed, along with measurements of N-terminal pro–brain natriuretic peptide.

Results: A total 89 patients (16.2%) had in-hospital HF assessed by Killip class > 1 in whom GLS was significantly impaired compared with patients without in-hospital HF (Killip class 1) (−14.6 ± 3.3% vs −10.1 ± 3.5%, $P < .0001$). In stepwise multiple logistic regression analysis including age, known HF, three-vessel disease, involvement of the left anterior descending coronary artery, episodes of atrial fibrillation, renal function, N-terminal pro–brain natriuretic peptide, troponin T level, LV ejection fraction, wall motion score index, and diastolic dysfunction indices, GLS emerged as the strongest marker of clinical HF (odds ratio, 1.47; 95% confidence interval [CI], 1.33–1.62; $P < .0001$). GLS remained independently associated with in-hospital HF in patients with LV ejection fractions > 40% (odds ratio, 1.33; 95% CI, 1.14–1.54; $P < .05$) and improved the C-statistic over other important covariates significantly (0.87 [95% CI, 0.82–0.91] vs 0.82 [95% CI, 0.76–0.89], $P = .02$).

Conclusions: Global longitudinal function assessed by GLS is significantly impaired in patients with MIs with in-hospital HF, and multivariate analysis suggests that reduced GLS is the single most powerful marker of manifest LV hemodynamic deterioration in the acute phase of MI. (J Am Soc Echocardiogr 2012;25:1280-9.)

Keywords: Myocardial infarction, Heart failure, Killip class, Mechanics, Echocardiography, Strain imaging

Modern reperfusion strategies have significantly decreased the loss of viable myocardium associated with acute myocardial infarction (MI), but in-hospital congestive heart failure (HF) remains a significant predictor of poor short-term and long-term prognoses.[1-3] Acute HF develops as a result of myocyte loss with depressed cardiac output and/or because of abnormally elevated filling pressure.[4,5]

Acute HF complicating MI despite preserved left ventricular (LV) ejection fraction (LVEF) is associated with a doubling in the risk for all-cause mortality.[5] The discrepancy between apparently minor acute myocardial injury and overt HF is poorly understood, but the burden of comorbid conditions adversely affecting myocardial relaxation properties, including hypertension, diabetes, and diffuse atherosclerosis, has been proposed to decrease the tolerance of even a minor loss of contractile function[4] that is not reflected by decreased LVEF. Deformation analysis using two-dimensional speckle-tracking allows the quantification of systolic longitudinal fiber shortening, which may be expressed as regional and global longitudinal strain (GLS). The longitudinal fibers in the subendocardial layer are more sensitive to ischemia and wall stress and can exhibit abnormal contraction patterns in the setting of apparently normal LVEF.[6] Furthermore, deformation properties of the myocardium in the setting of MI have been shown to correlate with infarct size.[7]

Echocardiographic findings in relation to in-hospital HF complicating MI with contemporary revascularization management are not well characterized. Recently, deformation analysis has been related to adverse prognosis in patients admitted with acute HF,[8] in those with ST-segment elevation MI (STEMI),[9] and in stable patients with chronic HF.[10] Furthermore, recent data suggest that patients with

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Abbreviations

AF = Atrial fibrillation

CI = Confidence interval

GLS = Global longitudinal strain

HF = Heart failure

IQR = Interquartile range

LAVi = Left atrial volume index

LV = Left ventricular

LVEF = Left ventricular ejection fraction

MI = Myocardial infarction

MR = Mitral regurgitation

MV = Mitral valve

PCI = Percutaneous coronary intervention

NSTEMI = Non–ST-segment elevation myocardial infarction

NT-proBNP = N-terminal pro–brain natriuretic peptide

STEMI = ST-segment elevation myocardial infarction

WMSI = Wall motion score index

HF with preserved ejection fraction are characterized by abnormal global LV longitudinal deformation.[11,12] To test the hypothesis that impaired GLS reflects in-hospital HF to a greater extent than traditional measures of systolic and diastolic dysfunction, we prospectively performed comprehensive echocardiographic analyses and neurohormonal assessment in a large cohort of patients with MIs. Furthermore, we assessed the importance of GLS in relation to in-hospital HF in patients with preserved LVEFs.

METHODS

Study Design and Patient Population

We conducted a prospective study of patients referred to our center for invasive coronary angiography for either STEMI or non–ST-segment elevation MI (NSTEMI) from September 2009 to October 2010. All patients provided written informed consent before transthoracic echocardiographic examination and blood sampling. Exclusion criteria were age < 18 years, noncardiac disease with a life expectancy < 1 year, or inability to provide written informed consent.

On the basis of hospital records obtained at admission, diabetes mellitus, hypertension, history of ischemic heart disease, prior MI, and preexisting congestive HF were registered. Findings in relation to coronary angiography, including culprit lesion, number of diseased vessels, left main coronary artery involvement, and type of revascularization (percutaneous coronary intervention [PCI], coronary artery bypass grafting, or no intervention) were registered. Clinical events from the arrival of emergency services and during hospitalization were recorded, including the occurrence of supraventricular arrhythmias. An episode of atrial fibrillation (AF) during hospitalization was registered as a complication related to the MI if there was no medical history of AF.

Peripheral samples of plasma were obtained within 24 hours of echocardiography. Analysis of N-terminal pro–brain natriuretic peptide (NT-proBNP) was performed on the commercially available Modular Analytics E170 NT-proBNP immunoassay (Roche Diagnostics GmbH, Mannheim, Germany) immediately after blood sampling. Additional biochemical workup included creatinine, hemoglobin, and peak troponin T during the hospital stay. Estimated glomerular filtration rate was measured using the four-variable Modification of Diet in Renal Disease equation.[13]

The primary outcome variable was in-hospital HF assessed according to the Killip classification as follows: no sign of HF (Killip class 1), basilar rales and/or radiologic signs of pulmonary congestion (Killip class 2), pulmonary edema (Killip class 3), and cardiogenic shock (Killip class 4).[14] Evidence of HF was assessed continuously throughout the admission both during daily rounds and by the trained staff members in the coronary care unit. An independent reviewer without knowledge of echocardiographic results adjudicated the diagnosis of HF. Timing of HF was classified as HF at presentation if patients had objective HF on admission or incident if HF developed after admission. For the present study, in-hospital HF was considered in all patients with Killip class > 1, whether on presentation or incident during hospitalization. Patients with known stable chronic HF, regardless of diuretic therapy before admission, were not included in the in-hospital HF group unless they experienced worsening decompensation. The study was approved by the regional scientific ethics committee (reference number H-D-2009-063).

Echocardiography and Two-Dimensional Speckle-Tracking

Echocardiography was performed within 48 hours of admission to our institution. Echocardiographic cine loops were obtained by recording three consecutive heart cycles. All examinations were performed using a Vivid e9 (GE Vingmed Ultrasound AS, Horten, Norway). Images were obtained at a frame rate of ≥60 frames/sec and digitally transferred to a remote workstation for offline analysis (EchoPAC BT 11.1.0; GE Vingmed Ultrasound AS). All analyses were performed by a single experienced operator (M.E.) without knowledge of Killip class and blinded to clinical, biochemical, and coronary angiographic information.

Two-dimensional parasternal images were used to determine LV dimensions and wall thickness. Maximum left atrial volume index (LAVi) was determined from the biplane area0length method just before the opening of the mitral valve (MV), and LV volumes were determined using the biplane Simpson model. Wall motion scoring was performed by dividing the left ventricle into 16 segments, and each segment was assigned a score on the basis of myocardial thickening (1 = normal or hyperkinesis, 2 = hypokinesis, 3 = akinesis). Wall motion score index (WMSI) was calculated from the average score of all segments. LV mass was calculated from the LV linear dimensions in the parasternal view. Volumetric and dimensional measurements of the left ventricle and left atrium were indexed to body surface area when appropriate. All volumetric analyses were performed in accordance with European Association of Echocardiography and American Society of Echocardiography recommendations.[15]

Color Doppler examination of the MV was performed in the apical window and if more than trivial mitral regurgitation (MR) was present, it was quantified by calculating the effective regurgitant orifice area using the proximal isovelocity surface area method. Effective regurgitant orifice area < 0.20 cm^2 was considered mild, 0.20 to 0.40 cm^2 moderate, and >0.40 cm^2 severe MR. If the effective regurgitant orifice area could not be determined, MR was considered mild when regurgitant jet area occupied >5% and <20% of the left atrial area, moderate when regurgitant jet area occupied >20% and <40%, and severe when regurgitant jet area occupied >40%. The presence of an eccentric jet raised the grade by one degree. Doppler recordings of mitral inflow were performed by placing a 2.5-mm sample volume at the tip of the MV leaflets during diastole and recording the pulsed-wave Doppler signal. Peak velocities of early (E) and atrial (A) diastolic filling and MV deceleration time were measured, and the E/A ratio was calculated. Continuous-wave Doppler recordings of the LV outflow tract were obtained, and aortic valve opening and closure times were measured. Pulsed-wave Doppler tissue imaging recordings were performed at the lateral and medial mitral annulus using a 2.5-mm

Table 1 Clinical and echocardiographic characteristics according to in-hospital congestive HF

Variable	All Patients (n = 548)	No HF (n = 459)	HF (n = 89)
Age (y)	63.2 ± 11.7	61.9 ± 11.4	69.9 ± 10.8*
Men	393 (71.6%)	337 (73.4%)	55 (61.8%)†
Killip class > 1	89 (16.2%)	0	89 (100%)
Episodes of AF	38 (6.9%)	21 (4.6%)	17 (19.1%)*
Medical history			
History of hypertension	253 (46.2%)	209 (45.5%)	44 (49.4%)
Smoking	368 (66.7%)	315 (68.6%)	53 (59.5%)
Ischemic heart disease	95 (17.3%)	79 (17.2%)	16 (18.0%)
Diabetes	75 (13.7%)	61 (13.3%)	14 (15.7%)
Known HF	33 (6.0%)	21 (4.6%)	12 (13.6%)†
eGFR (mL/min/1.73 m^2)	90.6 ± 28.6	92.8 ± 27.8	79.2 ± 30.3*
Peak troponin T (pg/L)	2.1 (0.5–5.5)	2.0 (0.5–4.6)	4.6 (0.6–9.7)*
NT-proBNP (pmol/L)	115.5 (48.3–246.0)	98.7 (42.4–187.0)	409.0 (187.0–732.0)*
Type of infarction			
STEMI	370 (67.5%)	307 (66.9%)	63 (70.8%)
NSTEMI	178 (32.5%)	152 (33.1%)	26 (29.2%)
Angiographic findings			
LAD involvement	208 (38.1%)	156 (34.0%)	52 (58.4%)*
Three-vessel disease or LM culprit	90 (16.2%)	67 (14.6%)	23 (25.8%)†
Treatment decision			
PCI	103 (18.8%)	82 (17.9%)	21 (23.6%)
Primary PCI	333 (60.8%)	284 (61.9%)	49 (55.1%)
No invasive treatment	112 (20.4%)	93 (20.3%)	19 (21.4%)
Additional CABG	44 (8.1%)	33 (7.2%)	11 (12.4%)
Echocardiography			
LVEF (%)	50.6 ± 10.7	52.1 ± 9.8	43.2 ± 12.2*
GLS (%)	−13.9 ± 3.7	−14.6 ± 3.3	−10.1 ± 3.5*
WMSI	1.46 ± 0.30	1.41 ± 0.27	1.75 ± 0.30*
Moderate to severe MR	3 (0.55%)	2 (0.44%)	1 (0.18%)
LAVi (mL/m^2)	35.9 ± 11.0	35.0 ± 10.1	40.7 ± 13.9*
MV deceleration time (msec)	179.9 ± 50.7	183.9 ± 49.6	158.8 ± 51.9*
E/e′ mean of lateral and medial	11.5 ± 5.3	10.8 ± 4.4	15.3 ± 7.8*

CABG, Coronary artery bypass grafting; *eGFR*, estimated glomerular filtration rate; *LAD*, left anterior descending coronary artery; *LM*, left main coronary artery.
Data are expressed as mean ± SD, as number (percentage), or as median (IQR).
*$P < .001$ and †$P < .05$ compared with patients without evidence of HF.

sample volume with measurements of myocardial peak early (e′). The mean E/e′ ratio was calculated from an average of lateral and medial values of E/e′.

Two-dimensional speckle-tracking was performed using a semiautomatic algorithm (Automated Function Imaging; GE Healthcare, Waukesha, WI). Briefly, manual positioning of three points (two annular and one apical) was performed in each of the three apical projections, enabling the software to semiautomatically track the myocardium throughout the heart cycle. Each ventricular wall was subsequently divided into three segments, for a total of 17 segments covering the entire myocardium. Careful inspection of tracking and manual correction, if needed, was performed, and in case of unsatisfactory tracking, the segment was excluded from the analysis. Longitudinal strain curves were generated for each segment, and from the average of all maximum values, GLS was calculated.

Statistical Analysis

All data are reported as mean ± SD or as median (interquartile range [IQR]). NT-proBNP was logarithmically transformed ($\log_{10}$) to stabilize the variance before entering the models. Categorical variables (presented as absolute values and percentages) were compared using χ^2 tests (or Fisher's exact tests when indicated). Continuous variables were compared using Student's t tests. All tests were two sided, and statistical significance was defined as $P < .05$. The variables included in multivariable logistic regression analysis to identify factors with independent associations with in-hospital HF were age as a continuous variable, sex, diabetes, known ischemic heart disease, known chronic HF, episodes of AF, presence of ST-segment elevation, left anterior descending coronary artery involvement, three-vessel disease and/or left main coronary artery involvement, peak troponin T, log NT-proBNP, estimated glomerular filtration rate, WMSI, LVEF, MR severity, E/e′, LAVi, MV deceleration time, and GLS. We performed the multiple logistic regression analyses using stepwise, forward, and backward elimination (stepwise method, with $P < .10$ for inclusion and $P < .05$ for retention). The performance of the final parsimonious model was assessed with the C-statistic. We also evaluated the added model performance with sequential addition to a baseline clinical model consisting of age, known chronic HF, episodes of AF, left anterior descending coronary artery involvement, three-vessel disease, peak troponin T,

Table 2 Univariate and multivariable logistic regression of in-hospital HF

Variable	Univariate			Multivariable*,†			
	χ^2	OR	95% CI	OR	95% CI	χ^2	*P*
Age (per year)	32.7	1.07	1.04–1.09	1.05	1.02–1.08	9.85	<.05
Female sex	4.9	1.72	1.07–2.77				
Known HF	9.6	3.26	1.54–6.91				NS
eGFR (per 10 mL/min/1.73 m^2 decrease)	16.32	1.21	1.10–1.32				NS
Episodes of AF	21.8	5.20	2.60–10.4	3.10	1.2–8.4	5.68	<.05
Three-vessel disease or LM culprit	5.8	1.97	1.14–3.40				NS
LAD involvement	17.1	2.67	1.68–4.25				NS
Peak troponin T (per 1 pg/L increase)	28.7	1.13	1.08–1.18	1.06	1.00–1.12	8.36	<.05
Log NT-proBNP (per 0.1 increase)	66.4	1.30	1.22–1–38				NS
LVEF (per 5.0% decrease)	45.5	1.49	1.33–1.68				NS
WMSI (per 0.1 increase)	72.7	1.54	1.39–1.69				NS
LAVi (per 1 mL/m^2 increase)	17.6	1.04	1.02–1.06	1.04	1.01–1.07	7.09	<.05
E/e′ ratio	39.8	1.14	1.09–1.18				NS
GLS (per absolute % increase)	77.3	1.50	1.37–1.64	1.47	1.33–1.62	45.5	<.0001

eGFR, Estimated glomerular filtration rate; *LAD*, left anterior descending coronary artery; *LM*, left main coronary artery.
Odds ratios are per 1-unit increase unless stated otherwise.
*C-statistic = 0.88, global χ^2 = 76.0.
†Hosmer and Lemeshow goodness-of-fit test, *P* = .45.

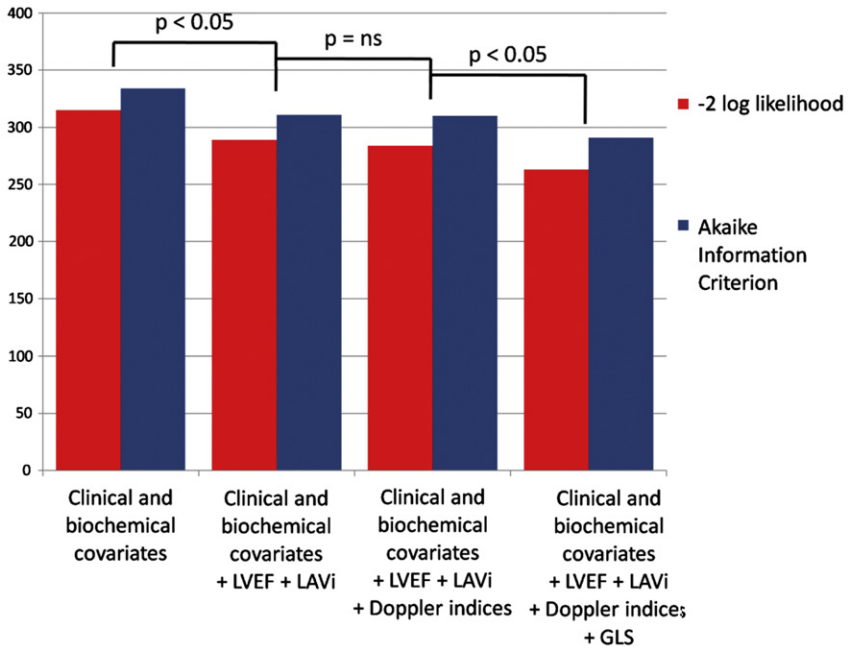

Figure 1 Incremental improvement in model performance as assessed by the −2 log likelihood and Akaike information criterion. Addition of LVEF and LAVi significantly improved a model including clinical information (age, history of heart failure, multivessel disease, left anterior descending coronary artery involvement, episodes of AF, troponin T, estimated glomerular filtration rate, and log NT-proBNP). Doppler indices (E/e′ ratio and MV deceleration time) did not improve the model, whereas the addition of GLS yielded significantly better model performance.

estimated glomerular filtration rate, and log NT-proBNP in the following sequence: (1) clinical model + LVEF + LAVi, (2) clinical model + LVEF + LAVi + E/e′ + MV deceleration time, and (3) clinical model + LVEF + LAVi + E/e′ + MV deceleration time + GLS. The incremental model performance was assessed with the Akaike information criterion and −2 log likelihood.

Furthermore, additional separate multiple logistic regression analyses were performed to identify echocardiographic and neurohormonal factors independently associated with in-hospital HF in patients with preserved LVEFs (>40%). Two separate multiple regression models were constructed for GLS and LVEF, but because of the small number of patients with in-hospital HF in this group, we

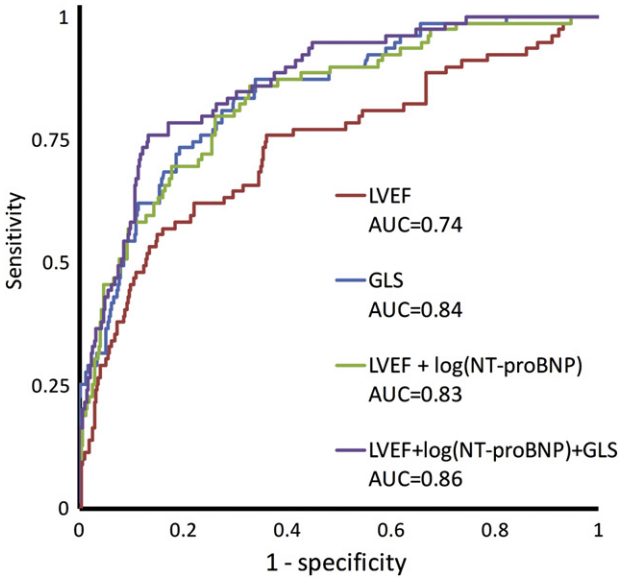

Figure 2 Receiver-operating characteristic curves depicting the performance of LVEF, LVEF plus log NT-proBNP, and GLS in relation to in-hospital HF. *AUC*, Area under the curve.

restricted the number of covariates to adjustment for age, NT-proBNP, troponin T, LAVi, and episodes of AF.

Internal validation was performed on the total study population by creating 200 bootstrap samples with random replacement. The stepwise model mentioned above was trained on each bootstrap sample, and the performance of each of these models was assessed in the original data set. The deviation between the C-statistic in the bootstrap sample and in the original data set was averaged for all 200 bootstrap samples and considered the average optimism. The C-statistic of the original parsimonious model was then corrected for the optimism and considered a nearly unbiased estimate of the internal validity. The variables selected by the stepwise modeling for each bootstrap sample were counted to identify factors that were consistently associated with in-hospital HF and to evaluate the stability of the modeling. SAS version 9.2 (SAS Institute, Inc., Cary, NC) was used for all data analyses.

RESULTS

Patient Population

The total study population consisted of 611 patients. Twenty-two patients were excluded from the analysis because of AF ($n = 18$) and ventricular paced rhythm ($n = 4$) during echocardiography. Forty-one patients were excluded because of poor image quality or technical limitations of echocardiography causing three or more myocardial segments to be incorrectly tracked by the speckle-tracking algorithm. Thus, 548 patients (90%) were included in the analyses (mean age, 63.2 ± 11.7 years; 71.6% men), of whom 89 (16.2%) had in-hospital HF as assessed by Killip class > 1. Incident HF was seen in 44 patients and HF on presentation in 45 patients. Among patients with STEMIs ($n = 370$ [67.5%]) and NSTEMIs ($n = 178$ [32.5%]), in-hospital HF was seen in 63 (17%) and 26 (15%) patients, respectively. Patients experiencing in-hospital HF were older, had more extensive myocardial injuries as assessed by peak troponin T, more often had left anterior descending coronary artery involvement, and had more in-hospital AF. The median duration of hospital stay was 5 days (IQR, 4–6 days). Patients with STEMIs were transferred directly to our institution after verification of ST-segment elevation on electrocardiograms taken by the emergency medical response team and electronically transmitted. If patients presented to local hospitals with ST-segment elevation, they were immediately transferred to our institution. In all cases, preprocedural treatment with antithrombotic therapy and heparin was initiated as soon as ST-segment elevation was diagnosed. The median symptom-to-balloon time was 197 min (IQR, 147–310 min). Patients with NSTEMIs were stabilized with antithrombotic therapy, β-blockade, and nitrates if indicated and transferred to our institution within 48 hours. The baseline clinical and echocardiographic characteristics are shown in Table 1.

Echocardiographic and Clinical Correlates of In-Hospital HF

Patients with in-hospital HF had significantly poorer longitudinal function (−10.1 ± 3.3% vs −14.5 ± 3.5%, $P < .0001$), lower LVEFs (43.2 ± 12.2% vs 52.1 ± 9.8%, $P < .0001$), and higher WMSIs (1.75 ± 0.30 vs 1.41 ± 0.27, $P < .0001$). Diastolic dysfunction was more frequent in patients with in-hospital HF with lower E/e′ ratios, shorter MV deceleration times, and larger values of LAVi (Table 1). Of the 89 patients with in-hospital HF, 52 were in Killip class 2, 27 in Killip class 3, and 10 in Killip class 4. There was progressive deterioration in GLS with increasing Killip class, and this was significant from Killip class 1 to 2 (−14.6 ± 3.3% vs −11.1 ± 3.3%, $P < .0001$) and class 2 to 3 (−11.1 ± 3.3% vs −8.3 ± 2.8%, $P < .005$), but there was no significant difference from class 3 to 4 after adjustment for multiple comparisons with Bonferroni correction. Patients with HF on presentation did not exhibit significantly different GLS (−10.3 ± 4.0% vs −9.8 ± 2.8%, P = NS) or LVEFs (44.2 ± 13.4% vs 41.8 ± 11.1%, P = NS) compared with patients with incident HF. Thus, multivariable modeling was conducted with in-hospital HF at any time as the dependent variable.

Significant independent predictors were consistently, in descending order of significance (on the basis of Wald χ^2 values), GLS, age, troponin T, LAVi, and episodes of AF (overall C-statistic = 0.87). The results of the multivariate logistic regression analysis with the significant independent predictors of in-hospital HF with associated odds ratios and 95% confidence intervals (CIs) are shown in Table 2. Analyzing STEMI and NSTEMI separately did not alter the results. Internal validation by bootstrapping of the overall model revealed minimal overoptimism (C-statistic = 0.84; optimism correction, 0.03) and confirmed GLS as the most important variable associated with in-hospital HF (selected in 99% of bootstrap samples).

The incremental value of GLS was assessed in four modeling steps shown in Figure 1. Addition of GLS decreased the Akaike information criterion and −2 log likelihood significantly ($P < .001$). In direct comparison the C-statistic of GLS outperformed that of LVEF (0.84 [95% CI, 0.79–0.88] vs 0.74 [95% CI, 0.65–0.78], $P < .0001$), and when adding NT-proBNP to LVEF, the C-statistic was still lower than for GLS alone, although the difference was not significant (0.83 [95% CI, 0.76–0.87] vs 0.84 [95% CI, 0.79–0.88], $P = .26$) (Figure 2).

In-Hospital HF in Patients with Preserved Ejection Fractions

A total of 464 patients (85%) had LVEFs > 40% (mean age, 62.4 ± 11.7 years; 72% men), of whom 53 (11.2%) experienced in-hospital HF. An example of a patient with a preserved LVEF, in-hospital HF, and impaired GLS is given in Figure 3. Significantly impaired GLS was seen in patients with in-hospital HF (−11.9 ± 2.9% vs −15.1

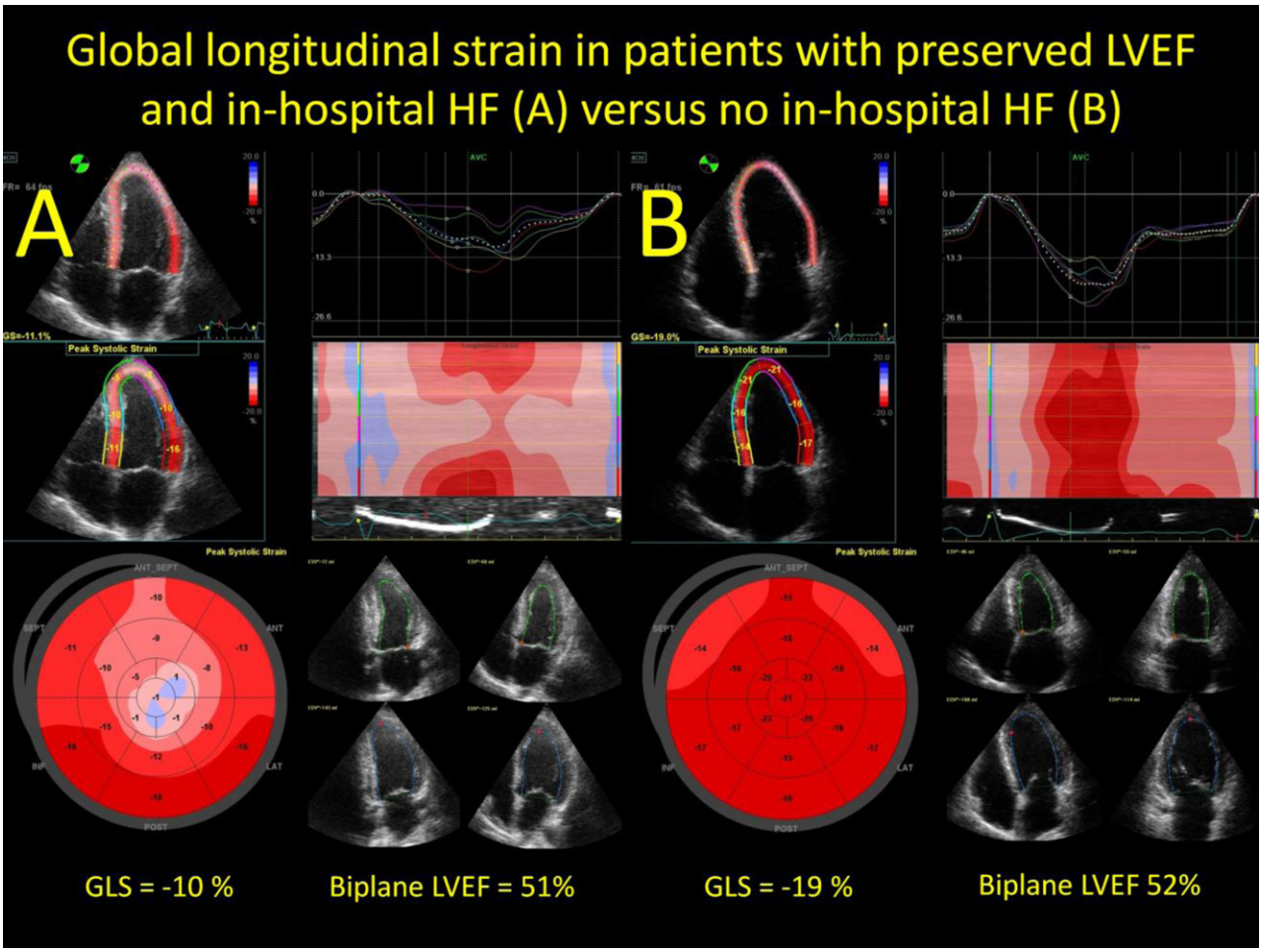

Figure 3 GLS and preserved LVEF in relation to in-hospital HF. This image demonstrates the severely impaired GLS of −10% in a patient with a preserved LVEF and pulmonary edema after MI **(A)** compared with a patient with preserved GLS, a normal LVEF, and an uneventful course after MI **(B)**.

± 3.0%, $P < .0001$), and median NT-proBNP levels were significantly higher (283.0 pmol/L [IQR, 164.0–599.0 pmol/L] vs 87.4 pmol/L [IQR, 37.2–160.0 pmol/L], $P < .0001$). Of the 53 patients with in-hospital HF, 38 were in Killip class 2, nine in Killip class 3, and five in Killip class 4. There was no significant difference in GLS from Killip class 2 to 3 (−11.9 ± 3.1% vs −11.3 ± 2.0%, P = NS) or class 3 to 4 (−11.3 ± 2.0% vs −13.1 ± 3.3%, P = NS). Clinical characteristics are shown in Table 3. Multiple regression analyses of in-hospital HF with age, troponin T level, log NT-proBNP, LAVi, and episodes of AF were performed with the addition of LVEF and GLS in two separate models. LVEF was not significant when log NT-proBNP was in the model, whereas GLS remained significant and diminished the association of log NT-proBNP to borderline significance (Table 4). When adding GLS to a model already consisting of age, troponin T, log NT-proBNP, LVEF, LAVi, and episodes of AF, the C-statistic increased significantly (0.82 [95% CI, 0.76–0.89] vs 0.87 [95% CI, 0.82–0.91], $P = .02$; Figure 4).

DISCUSSION

The main findings of this study are that impaired longitudinal myocardial function as assessed by GLS was significantly and independently related to in-hospital HF in patients with MI. Importantly, these findings were consistent in patients with preserved LVEFs, and the use of GLS rendered the association of NT-proBNP nonsignificant in this population. Eighty-nine patients (17%) experienced in-hospital HF, which is comparable with newer registry-based studies using PCI.[3,16] The prognostic importance of in-hospital HF after MI has been consistently demonstrated over two decades of evolving reperfusion and antiremodeling therapy, and assessment of Killip class constitutes an integral part of contemporary risk classification systems.[2,3] Early echocardiographic evaluation of LVEF is at the cornerstone of decision making after MI,[14,17] and several landmark trials have demonstrated benefit when targeting reduced LVEF combined with in-hospital HF,[18,19] but preserved LVEF does not preclude HF. This study is to our knowledge the first to show that impaired GLS is a strong marker of in-hospital HF in patients with MI. Furthermore, emerging evidence of abnormal systolic deformation parameters in patients with stable HF with preserved ejection fraction[20,21] is extended to a population with MI, in-hospital HF, and preserved LVEF, and these parameters seems more important than diastolic function even in this patient group.

GLS and In-Hospital HF

Strain imaging using two-dimensional speckle-tracking imaging theoretically overcomes the angle dependency and signal-to-noise ratio of

Table 3 Clinical characteristics according to in-hospital congestive HF and LVEF > 40%

Variable	No HF (n = 411)	HF (n = 53)
Age (y)	61.2 ± 11.5	69.18 ± 12.2*
Men	303 (72.7%)	30 (56.6%)†
Episodes of AF	19 (4.6%)	6 (11.3%)
Medical history		
History of hypertension	183 (55.5%)	26 (49.1%)
Smoking	285 (69.4%)	25 (47.2%)†
Ischemic heart disease	64 (15.7%)	5 (9.4%)
Diabetes	48 (11.7%)	8 (15.1%)
Known HF	13 (3.2%)	6 (11.3%)†
eGFR (mL/min/1.73 m^2)	93.2 ± 27.5	82.2 ± 30.0†
Peak troponin T (pg/L)	2.0 (0.52–4.43)	4.40 (1.27–9.70)*
NT-proBNP (pmol/L)	87.4 (37.2–160.0)	267.5 (162.0–599.0)*
Type of infarction		
STEMI	278 (67.6%)	40 (75.5%)
NSTEMI	133 (32.4%)	13 (24.5%)
Angiographic findings		
LAD involvement	133 (32.3%)	30 (56.6%)
Three-vessel disease or LM culprit	52 (12.6%)	9 (17.0%)
Treatment decision		
PCI	73 (19.8%)	15 (28.3%)
Primary PCI	259 (60.3%)	33 (62.2%)
No invasive treatment	79 (19.8%)	5 (9.4%)
Additional CABG	27 (5.7%)	3 (5.7%)
Echocardiography		
LVEF (%)	54.1 ± 7.8	51.5 ± 8.7
GLS (%)	−15.1 ± 3.0	−11.9 ± 2.9*
WMSI	1.37 ± 0.25	1.60 ± 0.27*
Moderate to severe MR	2 (0.4%)	0 (0%)
LAVi (mL/m^2)	34.8 ± 9.9	38.4 ± 12.3†
MV deceleration time (msec)	187.2 ± 48.7	172.0 ± 52.6
E/e′ mean of lateral and medial	10.4 ± 4.0	12.6 ± 5.6†

CABG, Coronary artery bypass grafting; *eGFR*, estimated glomerular filtration rate; *LAD*, left anterior descending coronary artery; *LM*, left main coronary artery.
Data are expressed as mean ± SD, as number (percentage), or as median (IQR).
*P < .001 and †P < .05 compared with patients without evidence of HF.

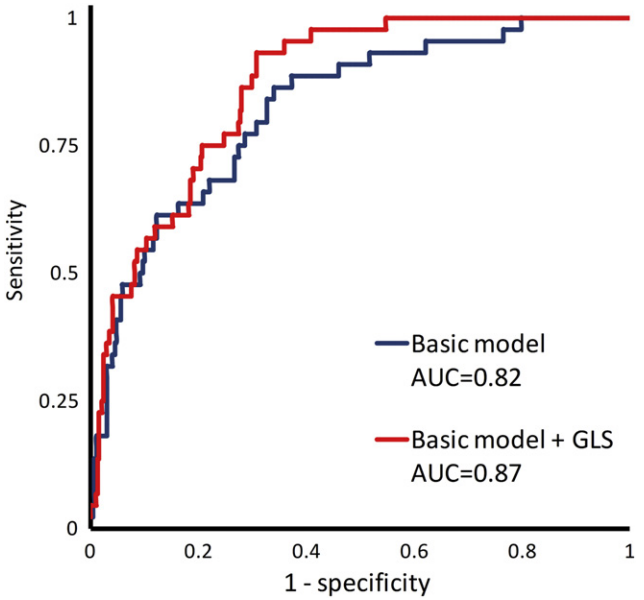

Figure 4 Receiver-operating characteristic curves depicting the improved model performance attained by adding GLS to a baseline model (age, episodes of AF, troponin T, LVEF, LAVi, and log NT-proBNP).

Doppler tissue imaging.[22] Assessment of GLS correlates with infarct size in MI[7] and with myocardial fibrosis in various cardiac diseases[23-25] and adds prognostic information in patients with stable chronic HF[8] and STEMIs.[9] Longitudinal deformation abnormalities have also been implicated in HF with preserved ejection fraction, suggesting that subtle systolic impairment may coexist with diastolic indices of impaired filling.[11,12]

In the present study, we observed the independent relation between GLS and in-hospital HF over and above clinical and biochemical covariates, including NT-proBNP, two-dimensional echocardiographic parameters, and Doppler indices of elevated LV filling pressure. Furthermore, GLS outperformed LVEF in direct comparison and was stronger than LVEF and NT-proBNP combined when assessing the C-statistic. Although GLS and LVEF are correlated, there are important mechanical differences, with LVEF primarily measuring radial thickening and to a lesser extent longitudinal motion. Myocardial wall thickening with the myocardium being incompressible is a consequence of circumferential and longitudinal fiber shortening. The subendocardial fiber layer is more sensitive to ischemia, and thus longitudinal deformation can be abnormal in various cardiac diseases before overt impairment of LVEF.

Coordinated action of longitudinal and circumferential fibers pulls the mitral plane downward in a twisting motion, thereby storing considerable elastic energy in the myocytes and interstitium. Early diastole is created by the pressure drop elicited by rapid untwisting and lengthening of the left ventricle, allowing rapid filling at low pressures.[22] Conversely, poor longitudinal systolic shortening will inherently allow less energy to be stored for release in early diastole, thus in effect contributing to diastolic impairment. This could explain why diastolic parameters, both isolated as E/e′ and MV deceleration time as well as in combination, did not emerge as predictors in multivariate analysis of in-hospital HF in the total study population.

The burden of comorbidities has been associated with the limited ability to compensate for acute dysfunction in an MI, with consequent hemodynamic deterioration. Thus, preexisting myocardial dysfunction could be reflected by impaired GLS, explaining the superiority of this measure compared with LVEF in relation to in-hospital HF. However, we also found that patients with in-hospital HF had higher peak troponin T levels, reflecting myocardial damage. Accordingly, a more precise estimation of infarct size as measured by GLS could also explain the superiority compared with LVEF. Overall, GLS outperformed LVEF, WMSI, and NT-proBNP, which are all collinear in nature; GLS had the largest χ^2 value among these covariates, and the addition of any of these to GLS yielded only marginal improvement in model performance.

We speculate that GLS may contribute information regarding the acute infarct-related injury as well as reflect the preexisting myocardial dysfunction, thereby strengthening the association with in-hospital HF. Finally, we demonstrated that when using GLS as

Table 4 Multiple logistic regression analysis of in-hospital HF in patients with LVEFs > 40%

Variable	LVEF model*			GLS model†		
	χ^2	OR	95% CI	χ^2	OR	95% CI
GLS (per absolute % increase)	—	—	—	13.9	1.33§	1.14–1.54
LVEF (per 5.0% decrease)	1.14	1.16‖	0.91–1.43	—	—	—
Age	4.49	1.04‡	1.01–1.08	5.94	1.05‡	1.01–1.09
Troponin T (per 1 pg/L increase)	8.47	1.11‡	1.04–1.19	5.66	1.08‡	1.01–1.16
Log NT-proBNP (per 0.1-unit increase)	9.29	1.16‡	1.06–1.28	1.43	1.10‖	0.99–1.22
Episodes of AF	0.21	0.74‖	0.21–2.61	0.37	0.67‖	0.18–2.43
LAVi (per 1 mL/m^2 increase)	2.26	1.02‖	0.99–1.06	3.35	1.03‖	0.99–1.07

Odds ratios are per 1-unit increase unless stated otherwise.
*Global χ^2 = 45.4, C-statistic = 0.83.
†Global χ^2 = 50.2, C-statistic = 0.86.
‡$P < .05$.
§$P < .001$.
‖P = NS.

a measure of LV systolic function, plasma levels of NT-proBNP did not contain additional information in multivariate analysis.

GLS and NT-proBNP in Patients with LVEFs > 40%

Fifty-three of 89 patients (60%) with in-hospital HF had preserved LVEFs, which is significantly higher compared with the proportion in the Valsartan in Acute Myocardial Infarction trial population.[26] We demonstrated that NT-proBNP is closely related to in-hospital HF, but even in this group, GLS rendered NT-proBNP borderline nonsignificant, suggesting that GLS contains more information than NT-proBNP in this setting. These findings suggest that analysis of longitudinal deformation may be of particular importance in patients with preserved LVEFs and in-hospital HF.

The prognostic role of natriuretic peptide release in patients with LVEFs > 40% after MI was found to be superior to LVEF in a large-scale study before the widespread implementation of PCI.[27] The overall prognostic value of natriuretic peptide release in MI is well established, but our results suggest that among patients with preserved LVEFs, a high-risk population with elevated NT-proBNP experiencing in-hospital HF is characterized by impaired longitudinal function. Although the number of HF events was small in this population, the addition of GLS measurements seemed to diminish the explanatory value of NT-proBNP. This suggests that GLS may be important in patients with apparently preserved LVEFs independently of NT-proBNP.

GLS in Relation to Timing and Severity of In-Hospital HF

In the present study, GLS was progressively impaired with worsening Killip class in the overall study population, although we could not detect a statistical difference from class 3 to 4, possibly because of the low incidence of cardiogenic shock in our population. In patients with preserved LVEFs, we found a significant difference in GLS between patients with and without in-hospital HF, but only a small and nonsignificant difference could be detected according to the severity of HF. This could be due to the smaller number of patients with in-hospital HF in the group with preserved LVEFs, lowering the statistical power to detect a true difference among the Killip classes. These results, together with the analyses of in-hospital HF as a single entity, point toward severe longitudinal fiber dysfunction as an important factor in the transition from myocardial injury toward HF in the acute phase of MI.

We found no significant differences in GLS or LVEF according to the timing of HF in this study, and we performed all analyses with in-hospital HF as one entity. Assessment of objective signs of in-hospital HF was performed on an ongoing basis in the semi-intensive setting of our coronary care unit and validated by an independent cardiologist without knowledge of the echocardiographic findings. Although GLS has been shown to steadily recover in many patients within 6 to 12 months after MI,[28] there is to the best of our knowledge no study to demonstrate significant acute fluctuations in LV longitudinal mechanics within days of MI. Furthermore, Gandhi *et al.*[29] showed that neither global myocardial function nor regional function as assessed by LVEF and WMSI, respectively, was significantly different during and after acute pulmonary edema. Thus, although the prediction of incident HF may be of highest relevance for clinicians in the short term during hospitalization, the highly significant association described in this study between hemodynamic deterioration at any time during the MI and impaired GLS increases our understanding of myocardial function in MI.

Study Limitations

There were some limitations to the present study. Echocardiography was performed within 48 hours of admission to our institution and not necessarily during the acute episode of HF, but it has been demonstrated that LV function during and after pulmonary edema is not significantly altered.[29] It is also possible that transient HF could have been overlooked during the course of hospitalization, even though patients were observed in a semi-intensive setting. We did not in the present study distinguish HF at presentation from incident HF during the hospital stay. This could be a significant limitation, because it has been shown that the timing of HF is associated with a mortality difference favoring patients with early symptoms.[3] However, most large randomized trials examining in-hospital HF as an inclusion criterion have not been concerned with this distinction,[19,26] so Killip class > 1 at any time during the course of MI is considered an indication for angiotensin-converting enzyme inhibition.[14] Furthermore, we found no significant difference among GLS, LVEF, and NT-proBNP when comparing HF on presentation with incident HF. Another limitation could be that all the patients with NSTEMIs in the present study were referred to our institution for coronary angiography according

to guidelines, so some selection bias was inherently present. Patients presenting with NSTEMIs in Denmark are routinely referred for subacute coronary angiography within 48 hours during hospitalization, but patients with severe comorbidities, short life expectancies, and known coronary disease not amenable to PCI or coronary artery bypass grafting are less likely to be subjected to invasive procedures. This limitation is not so clear in the case of acute STEMI, for which patients are triaged in a prehospital setting and directly referred to primary PCI without activating the local hospital.

Implications

Quantification of LV systolic function in the acute phase of MI remains integral in the prognostic evaluation. Measurement of GLS provides a rapid method of quantifying infarct extension and of estimating global reductions in longitudinal function. The present study suggests that reduced long-axis function may be a significant component in early HF during hospitalization for MI. Furthermore, the results suggest that in-hospital HF in patients with preserved LVEFs can be explained by reduced long-axis function independently of neurohormonal activation. Contemporary management of MI has increased the proportion of patients with only modestly impaired LVEFs. Early echocardiographic examination in patients with MIs could lead to increased attention to fluid overload and HF symptoms during and after the hospitalization in patients with impaired GLS. GLS could be important in selecting those patients with preserved LVEFs at high risk for future events. Long-term follow-up studies of patients with preserved LVEFs should be undertaken to assess whether the early assessment of GLS improves risk prediction in this large group of patients.

CONCLUSIONS

The results of this study demonstrate that GLS is significantly impaired in patients with MIs complicated by in-hospital HF. Measurements of GLS was superior to LVEF and NT-proBNP in providing information about myocardial dysfunction, suggesting that GLS is a powerful marker of hemodynamic deterioration in patients with MIs. In patients with preserved LVEFs, GLS provided more information than NT-proBNP in relation to in-hospital HF.

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