

## Abnormal Global Longitudinal Strain Predicts Future Deterioration of Left Ventricular Function in Heart Failure Patients With a Recovered Left Ventricular Ejection Fraction

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**Background**—Patients with recovery of left ventricular ejection fraction (LVEF) remain at risk for future deterioration of LVEF. However, there are no tools to risk stratify these patients. We hypothesized that global longitudinal strain (GLS) could predict sustained recovery within this population.

**Methods and Results**—We retrospectively identified 96 patients with a reduced LVEF <50% (screening echocardiogram), whose LVEF had increased by at least 10% and normalized (>50%) on evidence-based medical therapies (baseline echocardiogram). We examined absolute GLS on the baseline echocardiogram in relation to changes in LVEF on a follow-up echocardiogram. Patients with recovered LVEF had a wide range of GLS. The GLS on the baseline study correlated with the LVEF at the time of follow-up ( $r=0.33$ ;  $P<0.001$ ). The likelihood of having an LVEF >50% on follow-up increased by 24% for each point increase in absolute GLS on the baseline study (odds ratio, 1.24;  $P=0.001$ ). An abnormal GLS ( $\leq 16\%$ ) at baseline had a sensitivity of 88%, a specificity of 46%, and an accuracy of 0.67 ( $P<0.001$ ) as a predictor of a decrease in LVEF >5% during follow-up. A normal GLS ( $>16\%$ ) on the baseline study had a sensitivity of 47%, a specificity of 83%, and an accuracy of 0.65 ( $P=0.002$ ) for predicting a stable LVEF (−5% to 5%) on follow-up.

**Conclusions**—In patients with a recovered LVEF, an abnormal GLS predicts the likelihood of having a decreased LVEF during follow-up, whereas a normal GLS predicts the likelihood of stable LVEF during recovery. (*Circ Heart Fail.* 2017;10:e003788. DOI: 10.1161/CIRCHEARTFAILURE.116.003788.)

**Key Words:** cardiomyopathy, dilated ■ echocardiography ■ heart failure ■ left ventricular strain

Clinical studies have shown that medical and device therapies that reduce heart failure morbidity and mortality also lead to a reverse left ventricular (LV) remodeling and a return in LV ejection fraction (LVEF) to normal values.<sup>1-4</sup> Recent studies have shown that although many patients with a recovered LVEF seem stable clinically, they remain at increased risk for future heart failure events.<sup>5,6</sup> Indeed, whereas some patients with a recovered LVEF remain clinically stable for years, other patients will have recurrent heart failure events within months, even in the absence of a definable intercurrent event.<sup>7-9</sup> Although the basic mechanisms that are responsible for recurrent heart failure events in patients who appear clinically stable are not known, it is important to recognize that in most instances, reverse LV remodeling and recovery of LV function represents a reversion toward a normal myocardial phenotype but does not represent a normalization of the heart failure phenotype.<sup>10</sup> It has been suggested that one of the mechanisms responsible for recurrent heart failure events in patients with a recovered LVEF relates to the incomplete reversal of the heart failure

phenotype that arises secondary to irreversible end-organ myocardial damage in the failing heart.<sup>10</sup>

### See Clinical Perspective

At present, there are no validated clinical tools to identify patients with recovered LVEF who will remain clinically stable versus patients with recovered LVEF who will undergo recurrent heart failure events. Pertinent to this discussion, global longitudinal strain (GLS) has been shown to be more sensitive than LVEF as a measure of systolic function, and it has been used to identify subclinical LV dysfunction in patients with cardiomyopathies.<sup>11</sup> However, there are scant data with respect to the significance of GLS in patients with heart failure with recovered LVEF. Accordingly, we sought to characterize GLS in patients with recovered LVEF to determine whether assessment of GLS in hearts with recovery of LV function might be used to risk stratify patients who are more likely to undergo subsequent deterioration of LVEF and identify patients who are more likely to maintain a normal LVEF.

Received December 13, 2016; accepted April 24, 2017.

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The Data Supplement is available at <http://circheartfailure.ahajournals.org/lookup/suppl/doi:10.1161/CIRCHEARTFAILURE.116.003788/-/DC1>.

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DOI: 10.1161/CIRCHEARTFAILURE.116.003788

## Methods

This is a single-center, retrospective, longitudinal cohort study. The database for the Cardiac Diagnostic Laboratory at Barnes-Jewish Hospital was queried with respect to all patients studied between October 2011 and October 2015 who had a 2-dimensional transthoracic echocardiogram (TTE) with a documented LVEF <50% (referred to as the screening study). Among those patients with a screening LVEF <50%, we selected those patients for further study who had (1) an LVEF of >50% on TTE in the following calendar year (referred to as the baseline study) and (2) at least 1 additional TTE (referred to as the follow-up study) at any point after the baseline study. Patients were excluded from this analysis if they had a history of heart transplantation, left ventricular assist device (LVAD) implantation, an absolute improvement in LVEF <10% between the screening and baseline study, or atrial fibrillation on the baseline study. Of the 143 subjects that were identified, 47 were excluded for technical reasons (the echocardiographic machine used was not compatible with the strain analysis software used [29 patients] or poor image quality [18 patients]), leaving a final cohort of 96 patients. Clinical data for the final cohort of patients was extracted from the electronic medical record. The study was reviewed and approved by the Washington University in St Louis Institutional Review Board.

### 2D Echocardiographic Imaging and Speckle Tracking Echocardiography

Echocardiographic images were obtained using a Vivid 7 or Vivid E9 ultrasound machine (GE Healthcare) at Barnes-Jewish Hospital. All images were analyzed using ProSolv Cardiovascular software full (Fujifilm Medical Systems). The LV end-diastolic diameter (LVEDD) and end-systolic measurements were made in the parasternal long-axis view. The LVEF was calculated with the biplane method from apical views. The abovementioned measurements were performed by the Barnes-Jewish Hospital echo laboratory. Two-dimensional-speckle tracking measurements of GLS were performed in the 2-, 3-, and 4-chamber apical views by the research team using Echopac, version 12 (GE Healthcare). The endocardial border was traced manually at end systole. Tracking was adjusted to include the entire myocardial wall from the endocardium to the myoepicardial border. A segment was excluded if there was no visible motion of the speckles. All subjects included in the study had 3 apical views of sufficient quality to perform speckle tracking analysis with  $\leq 4$  of 18 segments excluded from the analysis. In the case of segment exclusion, the absolute GLS was calculated using a simple average of each acceptable segment in the 3 views. For this study, we defined a normal GLS as an absolute value of >16%.<sup>12</sup> All GLS measurements were performed by a single investigator, with a subset of  $\approx 50\%$  of the images reviewed and validated by a second reader. The intraobserver variability in GLS measurements was <10%.

### Statistical Analysis

All data are reported as mean $\pm$ SD. Baseline characteristics and medication use were compared between patients with a normal and abnormal GLS using Student 2-sample *t* test and Fisher exact test for continuous and categorical data, respectively. A repeated-measures analysis was conducted comparing echocardiographic measures across time. A mixed model methodology was used to include all available data and to account for between- and within-patient variation. After identification of an overall significant difference, all possible pairwise comparisons were made, and a Tukey adjustment was applied to control the overall type I error rate. The correlation between the LVEF and GLS on the baseline visit, as well as the correlation between GLS on the baseline study and the LVEF on the follow-up study, were assessed by the Pearson correlation coefficient. The accuracy of GLS as a predictor of decreased, unchanged, and increased LVEF during follow-up was calculated through a receiver operating characteristic curve considering GLS as a categorical variable being either normal or abnormal. Decreased LVEF was defined as >5% decrease in LVEF at follow-up; unchanged LVEF defined between -5% and +5%; and an increased LVEF was defined as change

of >5%. The association between GLS on the baseline visit and the LVEF on the follow-up visit was examined via an unadjusted logistic regression model that was later adjusted for LVEF on the baseline visit and for the number of days between the baseline and follow-up LVEF. The relationship between GLS as a continuous variable and negative changes in LVEF during follow-up was described using receiver operating characteristic curves. Data analysis was performed with SAS 9.4 (Cary, NC).

## Results

### Demographics of Patients With Recovered LVEF

The characteristics of the patients are shown in Table 1. The patient cohort was composed predominantly of men (56%), 57.8 $\pm$ 16.6 years of age, the majority of whom (76%) had nonischemic cardiomyopathy. At the time of the baseline 2D echocardiographic study, two thirds of the patients were receiving angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (64%) and  $\beta$ -blockers (69%), whereas 24% were receiving aldosterone antagonist. Table 2 shows that the screening LVEF was 37 $\pm$ 8%, with an LVEDD of 5.2 $\pm$ 0.89 cm and an LV end-systolic measurement of 3.4 $\pm$ 0.76 cm. The baseline study LVEF was 58 $\pm$ 6% ( $P$ <0.001 compared with screening LVEF), whereas the baseline LVEDD was 4.8 $\pm$ 0.84 cm ( $P$ =0.02 compared with screening LVEDD) and the LV end-systolic diameter was 3.4 $\pm$ 0.76 cm ( $P$ <0.001 compared with screening LVEDD). The time between the screening TTE and the baseline TTE with an LVEF >50% was 408 $\pm$ 223 days (median, 546 days; first quartile, 376 days; third quartile, 735 days).

### Assessment of Global LV Strain in Patients With Recovered LVEF

As shown in Figure 1A, the values for absolute LV-GLS in the baseline echocardiographic study of patients with a recovered LVEF ranged from 3% to 22%, with mean GLS of 14 $\pm$ 4%. Of note,  $\approx 35\%$  of the patients had a normal, absolute GLS (>16%), whereas  $\approx 65\%$  had reduced GLS ( $\leq 16\%$ ). The demographics of the patients with normal and abnormal GLS are also summarized in Table 1. As shown, the age, sex, frequency of ischemic cardiomyopathy, follow-up time, and use of heart

**Table 1. Characteristics of the Study Cohort**

	All Patients, n=96	aGLS >16%, n=28	aGLS $\leq$ 16%, n=68	<i>P</i> Value*
Men, %	56	54	50	0.82
Age at recovery, y	57.8 $\pm$ 16.6	53 $\pm$ 16.7	59.7 $\pm$ 17.2	0.07
Ischemic cardiomyopathy, %	34	18	36	0.09
Follow-up time, d	558 $\pm$ 248	604 $\pm$ 261	538 $\pm$ 241	0.24
ACEi/ARB at follow-up, %	64	60	65	0.65
Aldosterone antagonist at follow-up, %	24	25	23	1
$\beta$ -blocker at follow-up, %	69	57	74	0.14

ACEi indicates angiotensin-converting enzyme inhibitor; aGLS, absolute global longitudinal strain; and ARB, angiotensin receptor blocker.

\**P* values indicated comparison of patient characteristics in the aGLS  $\leq 16\%$  and a aGLS >16%.

**Table 2. Two-Dimensional Echocardiographic Assessment of Left Ventricular Structure and Function**

Variable	Screening	Baseline	Follow-Up	P Value
LVEF, %	36±8	59±6	52±12	<0.001
LVEDD, cm	5.2±0.90	4.8±0.84	4.9±0.77	0.001
LVESD, cm	4.1±0.96	3.4±0.77	3.5±0.74	<0.001

Echocardiographic variables for the 96 patients included in the study. The data are shown as mean±SD. Pairwise comparisons for all variables between screening and baseline have  $P<0.01$ . Pairwise comparison for baseline vs follow-up shows  $P<0.001$  for LVEF,  $P=0.72$  for LVEDD, and  $P=0.15$  for LVESD. LVEDD indicates left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; and LVESD, left ventricular end-systolic diameter.

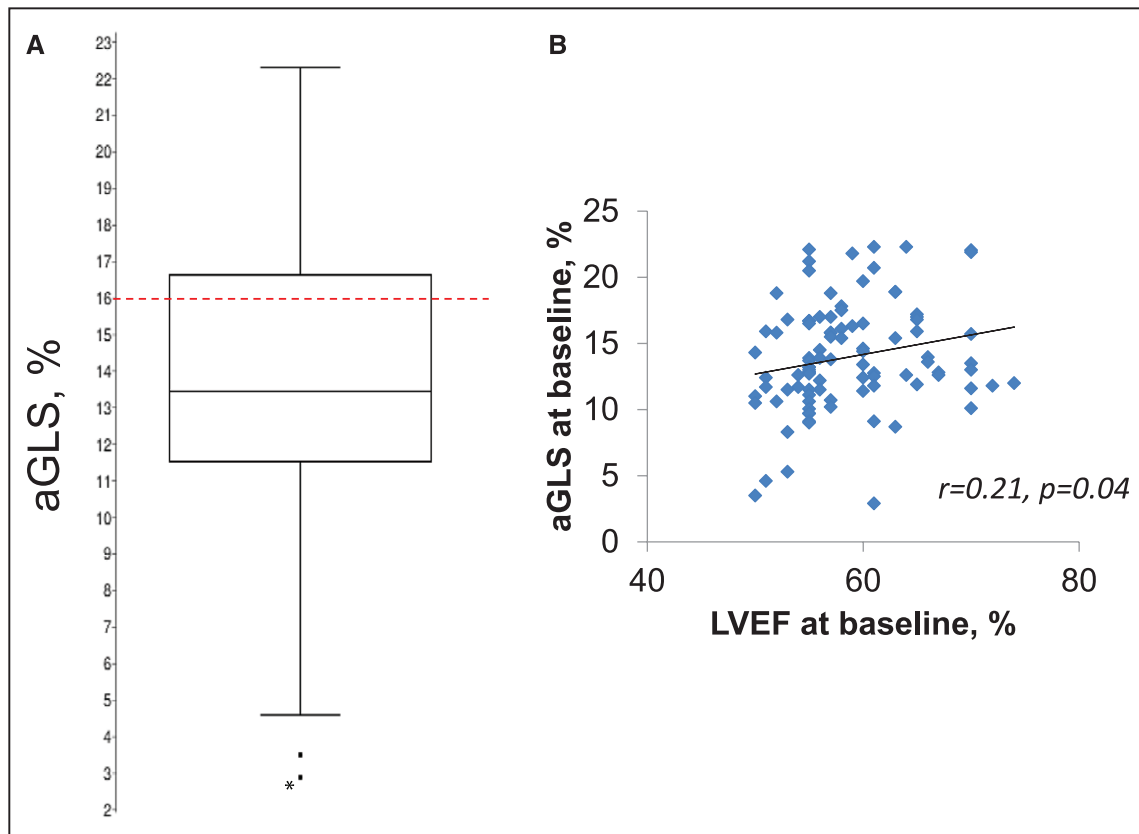
failure-related medications were not significantly different between groups. There was a statistically significant, although weak, correlation between the GLS and LVEF in the baseline echocardiographic study ( $r=0.21$ ;  $P=0.04$ ; Figure 1B).

### Correlation Between Global LV Strain at Baseline and LVEF at Follow-Up in Patients With Recovered LVEF

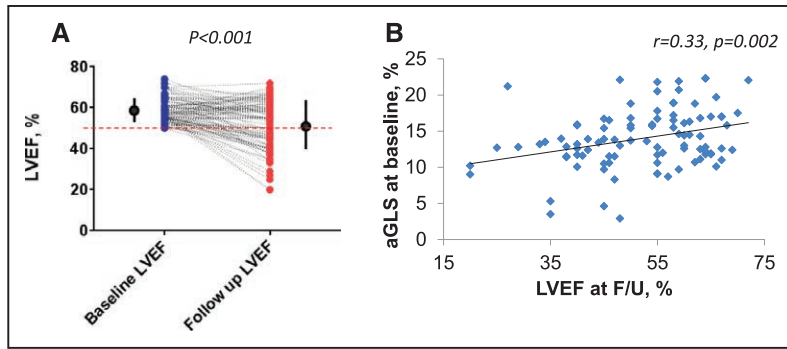
Figure 2A shows that there was a significant decline in LVEF for the patients evaluated in this study from baseline to follow-up (baseline LVEF,  $59\pm 6\%$  to follow-up LVEF,  $52\pm 12\%$ ;  $P<0.001$ ). The mean time between the baseline LVEF and the follow-up LVEF was  $558\pm 248$  days. Thirty-nine percent

of patients redeveloped an LVEF  $<50\%$  during follow-up. To determine whether the GLS on the baseline echocardiographic study correlated with future changes in LVEF, we examined the relationship between baseline GLS and the follow-up LVEF. Figure 2B shows that there was a significant correlation between the GLS and the LVEF at follow-up ( $r=0.33$ ;  $P<0.001$ ). Logistic regression modeling (Table 3) revealed that the likelihood of maintaining an LVEF  $>50\%$  at follow-up increased by 24% for each unit increase in GLS measured on the baseline echocardiographic study (unadjusted odds ratio [OR], 1.24; 95% confidence interval [CI], 1.09–1.41;  $P=0.001$ ). This relationship persisted even after adjusting for the baseline LVEF and for the time between baseline LVEF and the follow-up LVEF (OR, 1.22; 95% CI, 1.07–1.40;  $P<0.004$ ; Table 3).

To gain further insight into the association between GLS at baseline and the LVEF at follow-up, we arbitrarily divided the patients into 3 groups: decreased LVEF ( $<5\%$ ), unchanged LVEF ( $-5\%$  to  $+5\%$ ), and increased LVEF ( $>5\%$ ). As shown in Figure 3, patients with abnormal GLS at baseline were more likely to experience a decrease in LVEF during follow-up ( $P<0.001$ ). Forty-two of 68 patients (62%) with  $\text{GLS} \leq 16\%$  experienced a decrease in LVEF during follow-up, whereas only 6 of 28 patients (21%) with a normal GLS on the baseline study had a decreased LVEF during follow-up. An abnormal  $\text{GLS} \leq 16\%$  on the baseline study had sensitivity of 88%, a specificity of 46%, and an accuracy of 0.67 (95% CI, 0.58–0.75;



**Figure 1.** Global left ventricular strain in patients with recovered left ventricular ejection fraction (LVEF). **A**, Patients with recovered LVEF have a wide range of absolute global longitudinal strain (aGLS). Box and whisker plot of aGLS in patients with recovered LVEF is represented with a box-plot. **B**, Correlation of aGLS at baseline with LVEF on the baseline study ( $r=0.21$ ;  $P<0.04$ ). \*Outliers that fall 1.5× outside of the interquartile range. The horizontal red line marks the threshold for normal GLS  $>16\%$ .



**Figure 2.** Absolute global longitudinal strain (aGLS) at recovery correlates with left ventricular ejection fraction (LVEF) at follow-up. **A**, Changes in LVEF between the baseline and follow-up study. The respective values for the baseline and follow-up are connected by the black dotted lines. The dashed, horizontal red line marks LVEF of 50%. The LVEF on the follow-up study was significantly less than the LVEF on the baseline study ( $P < 0.001$ ), 39% of patients redeveloped an LVEF  $< 50\%$ , and 31% of patients developed an LVEF  $\leq 40\%$ . **B**, Correlation of aGLS at baseline with LVEF on the follow-up (F/U) study ( $r = 0.32$ ;  $P = 0.002$ ).

$P < 0.001$ ) as a predictor of a reduction in LVEF  $> -5\%$  during follow-up. In contrast, patients with normal GLS ( $> 16\%$ ) at baseline were more likely to maintain a stable LVEF (range,  $-5\%$  to  $+5\%$ ) during follow-up, than patients with an abnormal GLS at baseline ( $P = 0.002$ ). Eighteen of 28 patients (64%) with GLS  $> 16$  maintained a stable LVEF during follow-up, whereas only 20 of 68 patients (30%) with GLS  $\leq 16$  had no significant change in LVEF. A normal GLS on the baseline study had had a sensitivity of 47%, a specificity of 83%, and an accuracy of 0.65 (95% CI, 0.57–0.74;  $P = 0.002$ ) for predicting a stable LVEF on a follow-up study. There were only 10 patients in the study cohort who had an improvement in LVEF  $> 5\%$  on the follow-up study. The accuracy for GLS in terms predicting an improvement in LVEF was not statistically significant.

To further examine the use of using the baseline GLS to predict future changes in LVEF, we generated receiver operating characteristic curves to assess the relationship between GLS as a continuous variable and the likelihood of experiencing a reduction in LVEF of  $\geq 5\%$  and stable LVEF ( $-5\%$  to  $+5\%$ ) during follow-up. As shown in Figure 4, we found that GLS measured as a continuous variable correlated with future negative changes in LVEF during follow-up with an area under the curve of 0.68 (95% CI, 0.57–0.79;  $P < 0.001$ ) and with a stable LVEF during follow-up with an area under the curve of 0.65 (95% CI, 0.55–0.77;  $P = 0.005$ ).

**Table 3. Logistic Regression Model of the Relationship Between aGLS at Baseline and Sustained Recovery (Left Ventricular Ejection Fraction  $\geq 50\%$  at Follow-Up Study)**

	Unadjusted			Adjusted		
	OR	95% CI	P Value	OR	95% CI	P Value
GLS	1.24	1.09–1.41	0.001	1.22	1.07–1.40	0.004
LVEF at recovery	...	...	...	1.12	1.02–1.23	0.017
F/U time, per 10 d	...	...	...	0.99	0.97–1.01	0.14

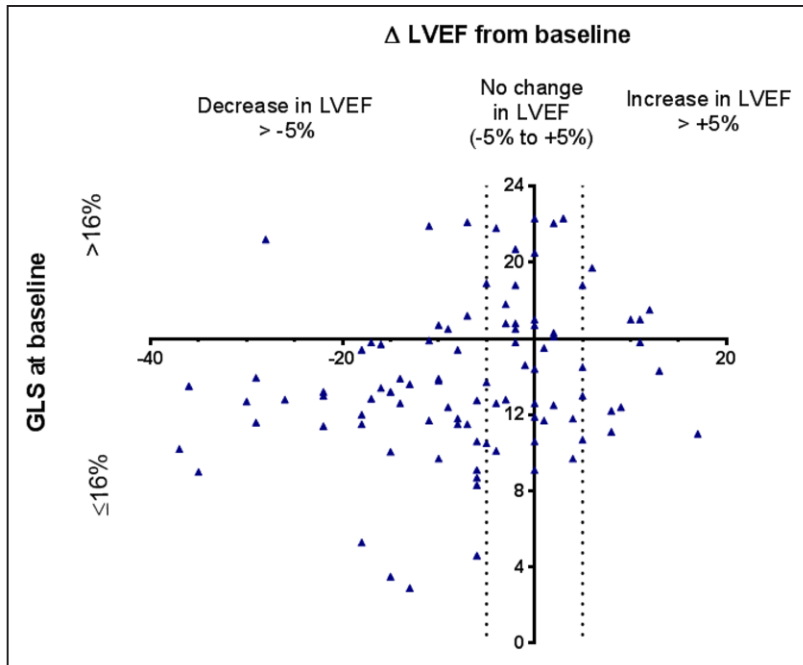
A logistic regression model of the relationship between absolute global longitudinal strain (aGLS) at baseline and sustained recovery was built using data from the 96 patients included in the study. The left half of the table shows the odds ratio for the unadjusted model. The right half of the table shows the odds ratio for the relationship between follow-up time and left ventricular ejection fraction (LVEF) at recovery in the third row; the odds ratio for the relationship between LVEF at recovery and LVEF in the follow-up study in the second row, and the relationship between GLS at recovery and LVEF in the follow-up study after correcting for the variables listed above in the first row. CI indicates confidence interval; F/U, follow-up; and OR, odds ratio.

As additional sensitivity analyses, we calculated the correlation between a GLS  $\leq 16\%$  in the baseline echocardiogram and a reduction in LVEF  $> 10\%$  during follow-up and found that GLS  $\leq 16\%$  predicted a negative change in LVEF of  $> 10\%$  with a sensitivity of 93%, a specificity of 39%, and an accuracy of 0.66 (95% CI, 0.56–0.74;  $P < 0.001$ ). In addition, we repeated all the described analyses using a more stringent definition of recovered ejection fraction and included only the 65 patients who had an LVEF  $\leq 40\%$  in the screening echocardiogram. Focusing only on this subgroup of 65 patients did not significantly change our findings. In fact, in this subcohort, we confirmed a significant correlation between GLS at baseline and LVEF at follow-up ( $r = 0.29$ ;  $P < 0.02$ ), and logistic regression modeling confirmed an increased chance of having an LVEF  $> 50\%$  at follow-up of a little  $> 20\%$  for each unit increase in GLS measured on the baseline echocardiographic study (unadjusted OR, 1.22; 95% CI, 1.05–1.42;  $P = 0.01$ ; Table I in the [Data Supplement](#)).

## Discussion

GLS is a direct echocardiographic assessment of myocardial fiber deformation<sup>13</sup> that has been previously shown to be a more sensitive measurement of myocardial dysfunction than LVEF,<sup>11</sup> and it has been shown to be a more powerful predictor of outcomes in patients with heart failure with a reduced ejection.<sup>14</sup> Furthermore, early changes in GLS after initiation of chemotherapy have been shown to be predictive of future LVEF decline.<sup>15</sup> However, to our knowledge, the prognostic value of GLS has not been evaluated in heart failure patients with a recovered LVEF.

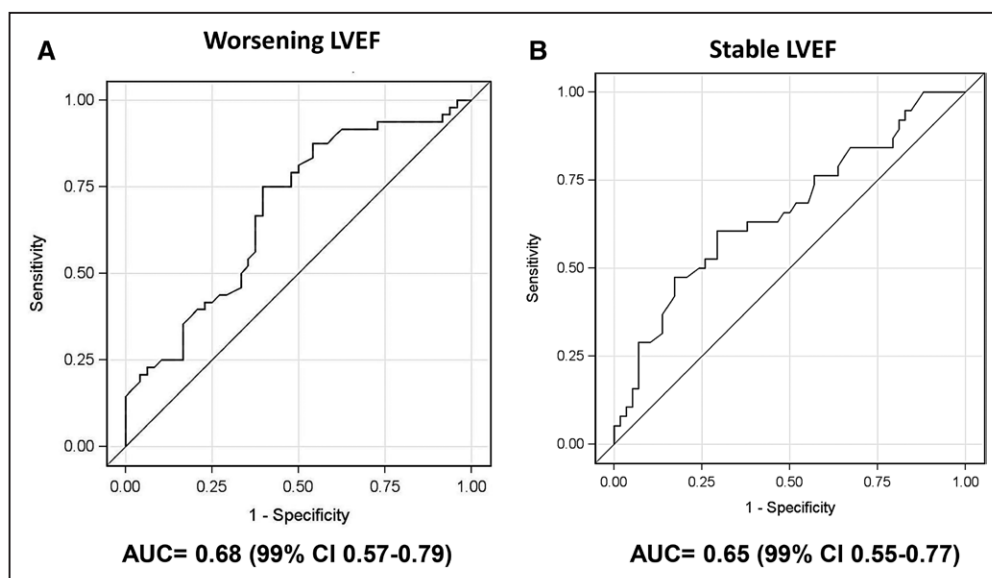
In the present study, examining absolute global LV strain (GLS) in heart failure patients who normalized their LVEF to  $> 50\%$ , we show that an abnormal GLS after recovery of LV function identifies subgroups of patients who are more likely to undergo subsequent deterioration of LVEF, whereas a normal value for GLS identifies patients who are more likely to maintain a normal LVEF. The following 3 observations support this statement. First, as shown in Figure 1A, heart failure patients with a recovered LVEF have a wide range of values for GLS, ranging from 3% to 22%, implying that there is a tremendous heterogeneity of intrinsic myocardial contractile function in heart failure patients who have normalized their LVEF. Although GLS was significantly correlated with LVEF on the baseline study, this correlation was relatively modest (Figure 1B), suggesting that GLS and LVEF measure complementary but different aspects of the myocardial contraction.



**Figure 3.** Relationship between absolute global longitudinal strain (GLS) on the baseline study and the change in left ventricular ejection fraction (LVEF) during follow-up. The change in LVEF at follow-up is displayed on the x axis, and the GLS is displayed on the y axis. The x axis and y axis were drawn to intersect at a normal value for GLS (ie, 16). All patients below the x axis had an abnormal value GLS ( $\leq 16\%$ ) on the baseline study, whereas all patients above the x axis had a normal GLS ( $>16\%$ ) on the baseline study. The 2 vertical dotted lines demarcate the changes in LVEF between  $-5\%$  to  $+5\%$ , which was arbitrarily defined as no change in LVEF. Patients to the left of the leftward vertical dotted line were defined as having a decreased LVEF during follow-up, whereas patients to the right of the rightward vertical dotted line were defined as having an increased LVEF during follow-up.

Whereas LVEF predominantly quantifies global radial contraction, GLS measures shortening of longitudinal myocardial fibers that are more sensitive to intrinsic changes in the myocardium, including myocardial fibrosis.<sup>11,16</sup> Second, when we evaluated the correlation between GLS at baseline and the change in LVEF at follow-up, we found that GLS at baseline correlated with LVEF at follow-up (Figure 3B), suggesting that the baseline GLS is related to changes in LVEF. Third, when we evaluated the prognostic significance of a GLS  $\leq 16\%$  versus GLS  $>16\%$ , we found that patients with an abnormal GLS on the baseline study were more likely to have a reduced LVEF on the follow-up study. Indeed, an abnormal GLS had

an accuracy of 0.67 for predicting a decrease in LVEF  $>5\%$ , whereas a normal GLS had an accuracy of 0.65 for predicting a stable LVEF ( $-5\%$  to  $+5\%$ ) during follow-up. When we performed a logistic regression model to evaluate the relationship between GLS on the baseline echocardiographic study and the likelihood of maintaining a normal LVEF during follow-up, the unadjusted OR suggested that the chance of having LVEF  $>50\%$  at follow-up increased 24% for each unit increase in GLS on the baseline LVEF (OR, 1.24; 95% CI, 1.09–1.41;  $P=0.001$ ; Table 3). Importantly, the OR was still significant after correcting for LVEF at baseline and time of follow-up, and our data remained essentially unchanged when we



**Figure 4.** Receiver operating curves (ROCs) for the relationship between absolute global longitudinal strain (aGLS) and left ventricular ejection fraction (LVEF) at follow-up. **A**, ROC curve for the relationship between aGLS as a continuous variable and the likelihood of experiencing a reduction in LVEF of  $>5\%$  at follow-up; area under curve (AUC) = 0.68 (95% confidence interval [CI], 0.57–0.79). **B**, ROC curve for the relationship between aGLS as a continuous variable and the likelihood of having a stable LVEF of  $-5\%$  to  $+5\%$  at follow-up; AUC=65 (95% CI, 0.55–0.77). CI indicates confidence interval.

performed a sensitivity analysis focusing only on a subcohort of patients who had an LVEF  $\leq 40\%$  at the time of screening (Table I in the [Data Supplement](#)).

### Recovery of LVEF

Reverse LV remodeling and recovery of LV function through the use of evidence-based medical therapies has become a major goal of contemporary medical therapy,<sup>3,17</sup> and indeed, patients whose heart undergoes reverse LV remodeling with an improvement in LVEF have improved clinical outcomes, when compared with patients whose hearts do not undergo reverse LV remodeling.<sup>18</sup> However, recent studies have shown that the patients with reverse LV remodeling and normalization of LVEF continue to experience heart failure admissions and heart failure deaths.<sup>6,19</sup> These and other observations in patients supported with LV-assisted devices have highlighted the importance of the differences between myocardial recovery, wherein patients remain free from future heart failure events, versus myocardial remission that is characterized by reverse LV remodeling and improved LVEF with recurrent heart failure admissions.<sup>10</sup> Basuray et al<sup>6</sup> have shown that patients with a recovered LVEF  $>50\%$  continue to experience heart failure admissions and heart failure deaths, suggesting that patients with a recovered LVEF represent a group of patients who have a milder but persistent heart failure phenotype. Similar findings were reported by Cheng et al.<sup>5</sup> Basuray et al posit that heart failure patients with recovered LVEF represent a spectrum of patients exhibiting reverse LV remodeling—a minority of whom have complete myocardial recovery—whereas the majority of patients have myocardial remission, with subsequent recurrent heart failure events. The results of the present study are entirely consistent with this point of view and demonstrate that patients with recovered LVEF have a wide spectrum of GLS values, suggesting that there is tremendous heterogeneity of intrinsic myocardial function in heart failure patients who have normalized their LVEF. Our results further suggest that measurement of GLS can help to stratify patients who have an underlying heart failure phenotype from patients who have a more complete reversal of the heart failure phenotype. To our knowledge, the literature reports only one study assessing GLS in patients with recovered LVEF.<sup>20</sup> In this work, the authors measured GLS in 37 patients and 11 normal controls and concluded that GLS was always reduced in patients with recovered LVEF when compared with controls.

Our work has several limitations that warrant further discussion. First, this study has all of the inherent limitations of retrospective single-center case-control study, and the generalizability of our findings will require independent corroboration. Second, although our study is 3 $\times$  larger than the only other study that measured LV strain in patients with a recovered LVEF,<sup>20</sup> the overall sample size is small for a heart failure study. Third, the length of follow-up was  $\approx 1.5$  years, and, therefore, it remains to be determined whether our findings would hold true with longer follow-up time. Fourth, our study was too small to highlight differences across subgroups of patients. Although we found that the prevalence of GLS  $\leq 16$  was  $\approx 2\times$  greater in patients with ischemic heart disease and recovered LVEF compared with patients with nonischemic

cardiomyopathy, this difference did not reach statistical significance. Nonetheless, we cannot exclude that these differences would have been significant statistically with a larger sample size. Fifth, although we know the medical regimen of patients around the time of the follow-up TTE, we do not have detailed information about the therapeutic choices that were done in between the baseline TTE and the follow-up TTE, and, therefore, we were unable to correct for continuation or discontinuation of medical therapy. Sixth, because of the retrospective nature of this study, we did not have biomarkers for all patients included in this study. Lastly, although we were unable to detect a statistically significant difference in use of heart failure medications among our groups of interest, only  $\approx 70\%$  of patients in our cohort were receiving  $\beta$ -blockers or angiotensin receptor blockers/angiotensin-converting enzyme inhibitors at follow-up; accordingly, it remains unclear whether the predictive accuracy of GLS would be as strong in a cohort of patients who remained on evidence-based medical therapies after normalization of LVEF. Thus, the results of the present study, although potentially important, must be regarded as provisional until they can be replicated independently by others.

### Conclusions

The major new finding of this study is that assessment of GLS in heart failure patients with a recovered LVEF identifies subgroups of patients who are more likely to undergo future deterioration of LV function and patients who are more likely to maintain a stable LVEF during follow-up. The finding that an abnormal GLS in patients with a recovered LVEF predicts subsequent deterioration of LV function is important scientifically insofar as these results support the point of view that, for many patients, reverse LV remodeling and recovery of LV function does not represent a full normalization of the abnormal biology of the failing heart.<sup>10</sup> This may explain why patients who appear clinically stable remain vulnerable to hemodynamic stress and undergo subsequent heart failure events.

The observed relationship between GLS and future deterioration of LV function may have potential clinical use. Should the findings of this study be confirmed in other patient cohorts, GLS could become part of the routine assessment of patients with recovered ejection fraction. However, given that the AUC for using GLS as a single predictor of a future deterioration of LVEF was 0.68, the results of the present study suggest that future studies will be needed to determine whether the use of other strain measures, or other imaging modalities (MRI, positron emission tomographic scanning, or fusion imaging) or biomarker panels, has added prognostic significance with respect to distinguishing patients with recovery of LVEF who will remain free from future heart failure events from patients with recovery of LVEF who are likely to experience recurrent heart failure events.

### Sources of Funding

Dr Lindman was supported by K23 HL116660 from the National Institutes of Health (NIH). Dr Adamo was supported by T32 HL007081 from the NIH. Dr Perry was supported by a scholarship of the American Heart Association.

### Disclosures

None.

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## CLINICAL PERSPECTIVE

Many patients with dilated cardiomyopathy recover a normal ejection fraction, either spontaneously or in response to medical and device therapies. However, patients with normalized ejection fraction remain at elevated risk for future cardiovascular events, and ≈40% of them experience a recurrence of left ventricular dysfunction. It has, therefore, been hypothesized that recovery of left ventricular ejection fraction (LVEF) does not reflect normalization in myocardial biology. We retrospectively measured global longitudinal strain (GLS) in a cohort of patients with normalized ejection fraction. Patients with normalized LVEF had a wide range of GLS values; moreover, GLS independently predicted the likelihood of redeveloping a depressed LVEF during follow-up. These findings suggest that normalization of LVEF does not necessarily correspond to normalization of the biology of the failing heart. Our findings also point at GLS as a useful tool for risk stratification of patients with recovered LVEF and normalized ejection fraction. Our findings in fact suggest that (1) among patients with normalized LVEF, patients with abnormal GLS (less negative than –16%) have 3× the risk of experiencing a drop in LVEF during follow-up (61.8% versus 21.4%) and (2) among patients with normalized LVEF, each point increase in GLS increases by 22% the likelihood of maintaining a normal range LVEF during follow-up, independently of LVEF at recovery and time of follow-up. However, validation of these findings in other patient cohorts is needed before routine implementation of these findings into clinical practice.

### **Abnormal Global Longitudinal Strain Predicts Future Deterioration of Left Ventricular Function in Heart Failure Patients With a Recovered Left Ventricular Ejection Fraction**

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*Circ Heart Fail.* 2017;10:

doi: 10.1161/CIRCHEARTFAILURE.116.003788

*Circulation: Heart Failure* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circheartfailure.ahajournals.org/content/10/6/e003788>

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**SUPPLEMENTAL MATERIAL**

**Supplementary Table 1 : Logistic Regression Model of the Relationship Between aGLS at Baseline and sustained recovery (LV Ejection Fraction  $\geq$  50% at follow-up study) in the sub-cohort of 65 patients with LVEF  $\leq$ 40% at baseline**

	Unadjusted			Adjusted		
	OR	95% CI	p	OR	95% CI	p
<b>aGLS</b>	1.22	1.05-1.42	0.01	1.20	1.02-1.41	0.025
<b>LVEF at recovery</b>	-	-	-	1.15	1.03-1.30	0.017
<b>F/U time (per 10 days)</b>	-	-	-	0.97	0.96-1.01	0.265

The left half of the table shows the odds ratio for the unadjusted model. The right half of the table shows in the third row the odds ratio for the relationship between follow-up time and LVEF at recovery, in the second row the odds ratio for the relationship between LVEF at recovery and LVEF in the follow-up study and in the first row the relationship between GLS at recovery and LVEF in the follow-up study after correcting for the variables above listed. (Key: LVEF = left ventricular ejection fraction; OR = odds ratio; CI= confidence interval).