CHAPTER 10

Global longitudinal strain predicts long-term survival in patients with chornic ischemic cardiomyopathy.

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ABSTRACT

Background. Left ventricular (LV) global longitudinal strain (GLS) is a measure of the active shortening of the LV in the longitudinal direction which can be assessed with speckle tracking echocardiography. The aims of this evaluation were to validate the prognostic value of GLS as new index of LV systolic function in a large cohort of patients with chronic ischemic cardiomyopathy and determine the incremental value of GLS to predict long-term outcome over other strong and well established prognostic factors.

Methods and Results. A total of 1060 patients underwent baseline clinical evaluation and transthoracic echocardiography. Median age was 66.9 years [interquartile range (IQR) 58.4, 74.2 years], 739 (70%) men. The median follow-up duration for the entire patient population was 31 months. During the follow-up, 270 patients died and 309 patients reached the combined end point (all-cause mortality and heart failure hospitalization). Compared to survivors, patients who died (270, [25%]) had larger LV volumes ($p<0.05$), lower LV ejection fraction ($p=0.004$), higher wall motion score index ($p=0.001$) and greater impairment of LV GLS ($p<0.001$). After dichotomizing the population based on the median value of LV GLS (-11.5%), patients with a LV GLS ≤-11.5% had superior outcome compared with patients with a LV GLS >-11.5% (log rank chi squared 13.86 and 14.16 for all-cause mortality and combined end point respectively, $p<0.001$ for both). On multivariate analysis, GLS was independently related to all-cause mortality (hazard ratio per 5% increase, 1.69, 95% CI 1.33-2.15; $p<0.001$) and combined end point (1.64, 95% CI 1.32-2.04; $p<0.001$).

Conclusions. The assessment of LV GLS with speckle tracking echocardiography is significantly related to long-term outcome in patients with chronic ischemic cardiomyopathy.

INTRODUCTION

Several studies have shown that various clinical, electrocardiographic (ECG), and echocardiographic parameters predict long-term outcome in patients with chronic ischemic cardiomyopathy.[1, 2] In patients with chronic ischemic cardiomyopathy, left ventricular (LV) ejection fraction (EF) and wall motion score index (WMSI) are well established predictors of long-term outcome.[3-7] However, both LVEF and WMSI have some limitations related to reproducibility, geometric assumption and expertise.

Recently new parameters derived from two-dimensional (2D) speckle tracking echocardiography permit the assessment of active myocardial deformation in multiple directions (radial, circumferential and longitudinal).[8-10] Particularly, the measurement of LV global longitudinal strain (GLS), which is a measure of the active shortening of the LV in the longitudinal direction, is more reproducible than LVEF and WMSI and does not rely on geometrical assumptions.[11-13]

Thus far, preliminary data suggest that LV GLS may be superior to LVEF and WMSI for the prediction of long-term outcome in different populations.[14] However, whether LV GLS is related to long-term outcome in patients with chronic ischemic heart disease is not established yet. Accordingly, the aims of this evaluation were to validate the prognostic value of LV GLS as new index of LV systolic function in a large cohort of patients with chronic ischemic cardiomyopathy, and determine the incremental value of LV GLS to predict long-term outcome over other strong and well established clinical, ECG and echocardiographic prognostic factors.

METHODS

Patient population and evaluation

The present evaluation consisted of retrospective analysis of clinical and echocardiographic data from patients with chronic ischemic heart disease. Patients with known coronary artery disease and prior myocardial infarction (>90 days prior to the index echocardiography) who underwent echocardiography between 1999 and 2009 were included in the present evaluation. This patient cohort formed part of ongoing institutional registries.[15, 16] Clinical and echocardiographic data were prospectively entered into the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center) and the echocardiography database, respectively. All patients received optimal medical treatment and coronary revascularization according to the current guidelines.[17, 18] In the present evaluation, atrial fibrillation, recent

myocardial infarction (< 90 days) and poor acoustic window resulting in inadequate speckle tracking analysis were exclusion criteria.

All patients underwent an extensive baseline clinical history and physical examination, 12-lead ECG and transthoracic echocardiography. Baseline clinical variables included New York Heart Association (NYHA) functional class, cardiovascular risk factors, medical treatment, and glomerular filtration rates (GFR) calculated by the Modification of Diet in Renal Disease formula as recommended by the National Kidney Foundation, Kidney Disease Outcomes Quality Initiative Guidelines.[19] Baseline echocardiographic variables included LV volumes, LVEF, WMSI, and LV GLS. All patients were prospectively followed up for the occurrence of death for any cause. From the various clinical, ECG and echocardiographic variables recorded, independent determinants of all-cause mortality were identified.

Echocardiography

Transthoracic echocardiography was performed with the patients at rest in the left lateral decubitus position with commercially available ultrasound equipment (M4S probe, Vivid 7, GE-Vingmed, Horten, Norway). All images were digitally stored on hard disks for offline analysis (EchoPAC version 108.1.5, GE-Vingmed, Horten, Norway).

LV end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated using Simpson's biplane method of discs. LVEF was calculated and expressed as a percentage. To calculate the WMSI, the LV was divided into 16 segments. A semiquantitative scoring system (1, normal; 2, hypokinesia; 3, akinesia; 4, dyskinesia) was used to analyze each study. Global WMSI was calculated by the standard formula: sum of the segment scores divided by the number of segments scored.[20]

Speckle tracking longitudinal strain analysis

In the present evaluation, global systolic LV myocardial function was determined with 2D speckle tracking strain analysis.[12, 21, 22] The speckle tracking software tracks the frame-to-frame movement of natural myocardial acoustic markers, or speckles, on standard gray scale images. Speckle tracking analysis is angle independent and allows accurate evaluation of myocardial deformation in all the LV segments.[8, 10] The change in length/initial length of the speckle pattern over the cardiac cycle is used to calculate longitudinal strain, with myocardial lengthening or stretching represented as positive strain, and myocardial shortening as negative strain.

To quantify LV GLS, 2D speckle tracking analyses were performed on standard routine grey scale images of the apical 2-, 4-chamber and long-axis views. During analysis, the endocardial border was manually traced at an end-systolic frame and the software traced automatically a region of interest that includes the entire myocardium. The width of the region of interest could be manually adjusted to ensure proper tracking of the myocardial wall. The software then automatically tracked natural myocardial acoustic markers and accepted segments of good tracking quality and rejected poorly tracked segments, while allowing the observer to manually override its decisions based on visual assessments of tracking quality. Results of the LV longitudinal strain analysis were automatically displayed as a 17-segment polar map model with 17 segmental/regional strain values and a mean global strain value for the entire LV (Figure 1).[12, 22, 23]

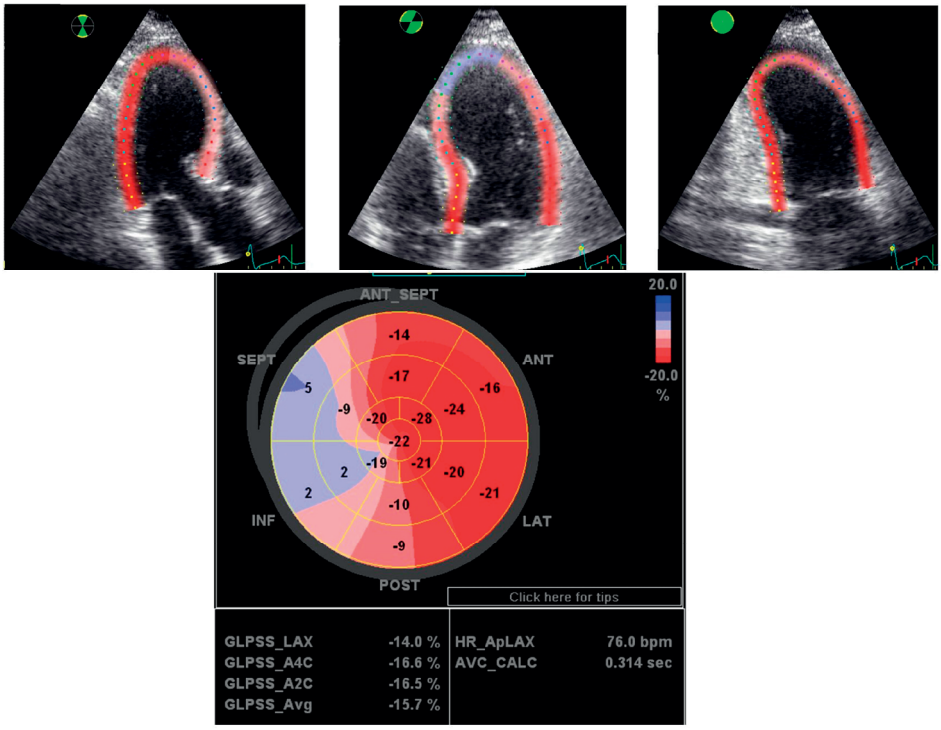

Figure 1. Example of assessment of global longitudinal myocardial strain (GLS) as provided by the EchoPAC software: apical long-axis view where the closure of aortic valve is defined (left upper panel), 4- (right upper panel) and 2-chamber (left lower panel) views. In the lower panel, the "bull's eye" plot, using a 17-segment model, provides the value of longitudinal strain for each segment of the left ventricle and the values of longitudinal strain of apical long-axis (GLPSS-LAX), 4-chamber (GLPSS_A4C), 2 chamber (GLPSS_A2C) and the value of GLS (GLPSS_Avg)

Previously reported intra- and inter-observer variabilities for LV GLS analysis expressed as mean absolute difference ± 1 standard deviation were 1.2 ± 0.5% and 0.9 ± 1.0% respectively.[22]

Follow-up and end points

Patients were followed up at 6- 12 monthly intervals according to protocol.[15, 16] Data on the occurrence of adverse events at follow-up were collected by reviewing medical records, retrieval of survival status through the municipal civil registries and telephone interviews. In the present evaluation, all-cause mortality and heart failure hospitalizations were recorded as event. Patients without data on the last 6 months were considered as lost to clinical follow-up. Data of these patients were included up to the last date of follow-up. From the various clinical, ECG and echocardiographic variables recorded, independent determinants of all-cause mortality were identified.

Statistical analysis

For uniformity reasons, continuous variables were presented as median and interquartile range (IQR). Categorical variables were presented as frequencies and percentages, and were compared using Chi-square test with Yates' correction. Mann-Whitney U test was used to compare unpaired continuous variables. Cumulative event rates from the time of inclusion were calculated using the Kaplan-Meier method for each independent predictor of all-cause mortality. The log-rank tests for time-to-event data with respect to the primary outcome were used for statistical comparison between 2 patient groups.

Multivariate Cox proportional-hazards models were constructed to identify independent clinical, ECG and echocardiographic determinants of all-cause mortality and combined end point. Univariate variables with a p-value <0.10 were entered as covariates using the stepwise backward likelihood ratio selection method. In all the analyses, the Cox proportional-hazards models were used to estimate hazard ratios and 95% confidence intervals for those independent variables. To avoid multicolinearity between the univariate predictors, a correlation coefficient of <0.7 (corresponding to a tolerance of >0.5) was set. The correlation coefficients between LV GLS and LVEF and WMSI were 0.87 and 0.85, respectively (both p<0.001) whereas the correlation coefficient between LVEF and WMSI was 0.88 (p<0.001). Accordingly, the independent predictive value of echocardiographic variables such as WMSI, LVEF and GLS was evaluated in different multivariate models. Finally, the incremental value of LV GLS to predict long-term outcome over WMSI and LVEF

was assessed by calculating the increment in Harrell's C concordance statistic.[24] A two-sided p value of < 0.05 was considered significant. All statistical analyses were performed using SPSS for Windows (SPSS Inc, Chicago), version 15 and STATA software (version 10.1, StataCorp, Texas).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

RESULTS

Patient population

Of the 1125 patients included, adequate echocardiographic analyses were feasible in 1060 (94%) patients (median age 66.9 years [IQR 58.4, 74.2 years], 739 [70%] men) and constituted the final patient population. The general characteristics of the overall patient population are reported in Table 1.

Hypertension, dyslipidemia and diabetes were present in 459 (43%), 440 (41%) and 298 (28%) patients, respectively. Most patients were treated with antiplatelets and/or oral anticoagulants (92%), beta-blockers (69%) and angiotensin converting enzyme inhibitors or angiotensin-receptor blockers (84%). In addition, 606 (57%) patients received an implantable cardioverter-defibrillator device. Furthermore, 32% underwent prior coronary-aorto bypass grafting whereas 25% underwent percutaneous coronary intervention. The remaining 43% of patients received optimal medical treatment. Table 2 summarizes the echocardiographic characteristics of the patient population. The median LVEDV, LVESV and LVEF were 140 ml (IQR 91-199 ml), 87 ml (IQR 39-150 ml), and 34% (IQR 25-58%), respectively. The median WMSI was 1.5 (IQR 1.0-2.0), and the median LV GLS was -11.5% (IQR -17.0 - -7.6%).

Survivors versus non survivors

The median follow-up duration for the entire patient population was 31.0 months (IQR 15.5, 52.7 months). A total of 270 (25%) patients died during the study duration and the median time to death was 25.9 months (IQR 13.0, 44.5 months). Differences in baseline clinical, ECG and echocardiographic variables between patients who died and patients who survived are outlined in Tables 1 and 2. Patients who died were more likely to be older (p <0.001) and diabetic (p <0.001), and to be in NYHA functional class III-IV (p <0.001). Interestingly, patients who died had lower hemoglobin (p =

Table 1. Clinical characteristics of overall population, and survivors versus non-survivors

	Overall population (n=1060)	Survivors (n=790)	Non-survivors (n=270)	p value
Demographic characteristics				
Age – years, median (IQR)	66.9 (58.4-74.2)	65.4 (56.8-72.6)	71.7 (64.0-76.7)	<0.001
Male gender – (%)	739 (70)	556 (70)	183 (68)	0.42
Body surface area – m^2, median (IQR)	1.97 (1.83-2.10)	1.97 (1.84-2.11)	1.95 (1.83-2.08)	0.24
Medical history				
NYHA functional class III-IV– (%)	420 (40)	282 (36)	138 (51)	<0.001
Hypertension – (%)	459 (43)	343 (43)	116 (43)	0.89
Dyslipidemia – (%)	440 (41)	338 (43)	102 (38)	0.15
Diabetes – (%)	298 (28)	199 (25)	99 (37)	<0.001
Current smoker – (%)	253 (24)	174 (22)	79 (29)	0.016
Family history ischemic heart disease – (%)	339 (32)	239 (30)	100 (37)	0.039
Systolic blood pressure - mmHg, median (IQR)	130 (112-150)	130 (115-150)	125 (110-148)	0.075
Diastolic blood pressure – mmHg, median (IQR)	77 (70-84)	77 (70-85)	75 (65-81)	0.030
Device therapy- (%)				
Implantable cardioverter-defibrillator	606 (57)	438 (55)	168 (62)	0.052
Cardiac resynchronization therapy	429 (40)	296 (37)	133 (49)	0.001
Revascularization- (%)				0.028
Percutaneous coronary intervention	269 (25%)	216	53	
Coronary-aorto bypass grafting	336 (32%)	243	93	
Medication at baseline – (%)				
Antiplatelets	627 (59)	477 (60)	150 (56)	0.16
Anticoagulants	446 (42)	314 (40)	132 (49)	0.009
Beta-blocker	740 (69)	545 (69)	195 (72)	0.32
ACE inhibitor or angiotensin-receptor blocker	896 (84)	671 (85)	225 (83)	0.53

Table 1. Clinical characteristics of overall population, and survivors versus non-survivors (continued)

	Overall population (n=1060)	Survivors (n=790)	Non-survivors (n=270)	p value
Calcium channel blocker	199 (19)	142 (18)	57 (21)	0.25
Diuretic	662 (62)	472 (60)	190 (70)	0.002
Nitrate	208 (20)	136 (17)	72 (27)	0.001
Statin	774 (73)	583 (74)	191 (71)	0.33
Laboratory measure at baseline				
Hemoglobin – g/dL, median (IQR)	13.9 (12.6-14.8)	14.0 (12.7-14.8)	13.7 (11.9-14.5)	0.004
Estimated GFR – mL/min/1.73m^2, median (IQR)	66.8 (51.3-82.8)	71.8 (57.0-85.2)	53.7 (39.7-67.0)	<0.001
Electrocardiogram at baseline				
Heart rate – beats/min, median (IQR)	70 (61-80)	70 (61-80)	73 (63-82)	0.005
QRS duration – ms, median (IQR)	100 (100-146)	100 (100-142)	116 (100-154)	0.001

ACE: angiotensin converting enzyme; IQR: interquartile range; NYHA: New York Heart Association;

0.004) and GFR (p <0.001). In addition, they had a higher heart rate (p = 0.005) and wider QRS complex (p = 0.001). Regarding echocardiographic parameters, patients who died had larger LVEDV (p = 0.012) and LVESV (p = 0.005) and lower LVEF (p = 0.004). Finally, patients who died had higher WMSI (p = 0.001) and a greater impairment of LV GLS (p <0.001).

Table 2. Echocardiographic characteristics of overall population, and survivors versus non-survivors

	Overall population (n=1060)	Survivors (n=790)	Non-survivors (n=270)	p value
Echocardiography at baseline				
Wall motion score index, median (IQR)	1.5 (1.0-2.0)	1.5 (1.0-1.9)	1.6 (1.0-2.1)	0.001
LVEF – %, median (IQR)	34 (25-58)	35 (26-59)	33 (22-56)	0.004
LVEDV – ml, median (IQR)	140 (91-199)	136 (90-195)	153 (94-225)	0.012
LVESV – ml, median (IQR)	87 (39-150)	84 (36-142)	100 (42-170)	0.005
GLS – %, median (IQR)	-11.5 (-17.0- -7.6)	-12.3 (-17.5- -8.5)	-9.8 (-15.3- -6.5)	<0.001

GLS: global longitudinal left ventricular strain; IQR: interquartile range; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume.

Follow-up

Kaplan-Meier curves for LV GLS of all-cause mortality in ischemic cardiomyopathy patients are reported in Figure 2A. Particularly, when the patient population was dichotomized based on the median LV GLS (-11.5%), a cumulative 4%, 10% and 17% of patients with a LV GLS ≤-11.5% (less impaired LV shortening) died by 1, 2 and 3 years follow-up respectively. In contrast, a respective 7%, 17% and 27% of patients with a LV GLS >-11.5% (more impaired LV shortening) died during the same time period (log rank chi squared = 13.86, p <0.001; Figure 2A).

In addition, the combined end point (heart failure hospitalization and all-cause mortality) was reached by 309 patients during the follow-up. Kaplan-Meier estimates of the time to the combined end point for patients with an LV GLS ≤-11.5% and patients with an LV GLS >-11.5% are indicated in Figure 2B. After 3 years of follow-up, the cumulative free survival rates of combined end point in the group of patients with an LV GLS ≤-11.5% were 6%, 13% and 20% at 1, 2 and 3 years follow-up, respectively. In contrast, the group of patients with an LV GLS >-11.5% showed cumulative free survival rates of combined end point of 10%, 20% and 29% at 1, 2 and 3 years follow-up, respectively (log rank chi squared = 14.16, p<0.001; Figure 2B).

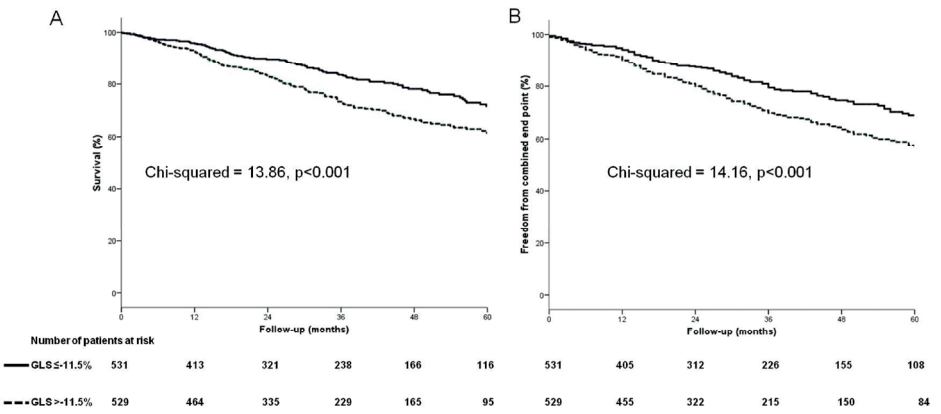

Figure 2: Kaplan Meier estimates of all-cause mortality (panel A) and combined end point (panel B). The cumulative survival rates were compared between patients with left ventricular GLS ≤-11.5% (solid line) and patients with GLS >-11.5% (dotted line).

Predictors of all-cause mortality and combined end point

To identify predictors of all-cause mortality, univariate Cox analyses were performed. First, among various clinical and ECG variables, the independent determinants were

identified (Table 3). Age, diabetes mellitus, hemoglobin and renal function (measured with GFR) were independent determinants of all-cause mortality. Next, several echocardiographic variables of LV function were introduced in different multivariate models to evaluate their prognostic value (Table 4). WMSI (HR 1.43, 95% CI 1.14-1.79; p=0.002), LVEF (HR 1.04, 95% CI 1.00-1.08; p=0.026) and LV GLS (HR 1.69, 95% CI 1.33-2.15; p<0.001) were significantly associated with all-cause mortality. However, the model including LV GLS had the best relative fit and LV GLS provided the highest Harrell's C concordance statistics (Table 5).

In addition, the clinical and ECG variables that were independently associated with the combined end point (heart failure hospitalization and all-cause mortality) were age, diabetes mellitus and renal function. The predictive value of WMSI, LVEF and LV GLS was evaluated in different multivariate Cox regression analyses to avoid multicolinearity. WMSI (HR 1.44, 95% CI 1.16-1.78; p=0.001), LVEF (HR 1.04, 95% CI 1.00-1.08; p=0.009) and LV GLS (HR 1.64, 95% CI 1.32-2.04; p<0.001) were independent predictors of the combined end point (Table 4). In addition, the model including LV GLS had the highest Harrell's C statistic (Table 5).

Table 3. Cox uni- and multivariable regression analysis to identify clinical predictors of all-cause mortality and combined end point during follow-up

Dependent variable: Death from any cause	**Univariable analysis**		**Multivariable analysis**	
	HR (95% CI)	**p value**	**HR (95% CI)**	**p value**
Independent variables				
Age – years	1.05 (1.03-1.06)	<0.001	**1.04 (1.03-1.06)**	**<0.001**
NYHA functional class III-IV	1.79 (1.41-2.28)	<0.001	1.23 (0.92-1.66)	0.164
Diabetes	1.60 (1.25-2.05)	<0.001	**1.49 (1.15-1.92)**	**0.002**
Diastolic blood pressure, per 10 mmHg increase	0.98 (0.97-0.99)	<0.001	0.94 (0.84-1.04)	0.227
Cardiac resynchronization therapy	1.73 (1.38-2.16)	0.002	1.32 (0.88-1.98)	0.177
Anticoagulants	1.33 (1.04-1.68)	0.021	1.13 (0.87-1.47)	0.350
Diuretics	1.55 (1.19-2.02)	0.001	0.96 (0.71-1.31)	0.815
Nitrates	1.45 (1.11-1.90)	0.009	1.23 (0.93-1.62)	0.144
Hemoglobin, per 1 g/dl decrease	1.36 (1.06-1.22)	<0.001	**1.08 (1.01-1.16)**	**0.043**
GFR, per 10 ml/min/1.73m^2 decrease	1.02 (1.02-1.03)	<0.001	**1.15 (1.09-1.22)**	**<0.001**
Heart rate, per 5 beats/min increase	1.05 (1.00-1.09)	0.030	...	...
QRS duration, per 20 ms increase	1.03 (0.99-1.07)	0.060	...	...

Table 3 (continued)

Dependent variable: Combined end point	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Independent variables				
Age – years	1.04 (1.02-1.05)	<0.001	**1.03 (1.01-1.04)**	**<0.001**
NYHA functional class III-IV	1.63 (1.33-2.03)	<0.001	...	...
Diabetes	1.37 (1.08-1.74)	0.009	**1.30 (1.02-1.66)**	**0.034**
Diastolic blood pressure, per 10 mmHg increase	0.88 (0.80-0.96)	0.007	...	...
Cardiac resynchronization therapy	1.45 (1.15-1.81)	0.001	...	...
Anticoagulants	1.26 (1.01-1.58)	0.043	...	...
Diuretics	1.40 (1.10-1.78)	0.006	...	...
Nitrates	1.34 (1.04-1.73)	0.025	...	...
Hemoglobin, per 1 g/dl decrease	1.12 (1.04-1.20)	0.001	...	...
GFR, per 10 ml/min/1.73m^2 decrease	1.20 (1.14-1.26)	<0.001	**1.15 (1.09-1.22)**	**<0.001**
Heart rate, per 5 beats/min increase	1.04 (0.99-1.08)	0.072	...	...
QRS duration, per 20 ms increase	1.03 (1.00-1.07)	0.041	...	...

CI: confidence intervals; GFR: glomerular filtration rate; HR: hazard ratio; NYHA: New York Heart Association

Table 4. Cox uni- and multivariable regression analysis to identify echocardiographic predictors of all-cause mortality during follow-up

Dependent variable: All-cause mortality	Multivariable analysis		-2 log Likelihood
	HR (95% CI)	p value	
Independent variables: clinical + WMSI			**3226.8**
Age – years	**1.04 (1.03-1.06)**	**<0.001**	
Diabetes	**1.55 (1.21-1.99)**	**<0.001**	
Hemoglobin, per 1 g/dl decrease	**1.08 (0.99 -1.16)**	**0.059**	
GFR, per 10 ml/min/1.73m^2 decrease	**1.17 (1.05-1.24)**	**<0.001**	
WMSI	**1.43 (1.14-1.79)**	**0.002**	
Independent variables: clinical + LVEF			**3231.6**
Age – years	**1.04 (1.03-1.06)**	**<0.001**	
Diabetes	**1.59 (1.23-2.04)**	**<0.001**	

Table 4 (continued)

Dependent variable: All-cause mortality	**Multivariable analysis**		**-2 log Likelihood**
	HR (95% CI)	**p value**	
Hemoglobin, per 1 g/dl decrease	**1.08 (0.99-1.16)**	**0.048**	
GFR, per 10 ml/min/1.73m^2 decrease	**1.16 (1.10-1.24)**	**<0.001**	
LVEF, per 5% decrease	**1.04 (1.00-1.08)**	**0.026**	
Independent variables: clinical + GLS			**3215.9**
Age – years	**1.04 (1.03-1.06)**	**<0.001**	
Diabetes	**1.60 (1.24-2.05)**	**<0.001**	
Hemoglobin, per 1 g/dl decrease	**1.08 (1.00-1.16)**	**0.043**	
GFR, per 10 ml/min/1.73m^2 decrease	**1.15 (1.09-1.22)**	**<0.001**	
GLS, per 5% increment	**1.69 (1.33-2.15)**	**<0.001**	
Dependent variable: Combined end point	**Multivariable analysis**		
	HR (95% CI)	**p value**	**-2 log Likelihood**
Independent variables: clinical + WMSI			**3733.3**
Age – years	1.03 (1.02-1.04)	<0.001	
Diabetes	1.37 (1.08-1.74)	0.010	
GFR, per 10 ml/min/1.73m^2 decrease	1.15 (1.09-1.21)	<0.001	
WMSI	1.44 (1.16-1.78)	0.001	
Independent variables: clinical + LVEF			**3737.3**
Age – years	1.03 (1.02-1.04)	<0.001	
Diabetes	1.34 (1.06-1.70)	0.016	
GFR, per 10 ml/min/1.73m^2 decrease	1.16 (1.10-1.22)	<0.001	
LVEF, per 5% decrease	1.04 (1.01-1.08)	0.009	
Independent variables: clinical + GLS			**3724.2**
Age – years	1.03 (1.02-1.04)	<0.001	
Diabetes	1.37 (1.08-1.74)	0.010	
GFR, per 10 ml/min/1.73m^2 decrease	1.14 (1.08-1.21)	<0.001	
GLS, per 5% increment	1.64 (1.32-2.04)	<0.001	

CI: confidence intervals; GFR: glomerular filtration rate; GLS: global longitudinal left ventricular strain; HR: hazard ratio; LVEF: left ventricular ejection fraction; WMSI: wall motion score index.

Table 5. Incremental prognostic value of LV GLS: discrimination indices analysis.

Model	All-cause mortality	Harrell's C-concordance statistic index
1	Clinical parameters + WMSI	0.689
2	Clinical parameters + LVEF	0.686
3	Clinical parameters + GLS	0.700
Model	Combined end point	Harrell's C-concordance statistic index
1	Clinical parameters + WMSI	0.653
2	Clinical parameters + LVEF	0.648
3	Clinical parameters + GLS	0.659

GLS: global longitudinal left ventricular strain; HR: hazard ratio; LVEF: left ventricular ejection fraction; WMSI: wall motion score index.

DISCUSSION

The main findings of the present study were as follows: 1) LV GLS was significantly related to long-term outcome; 2) the predictive model including LV GLS provided the best relative fit and, finally, 3) LV GLS was independently related to all-cause mortality and combined end point and had prognostic incremental value over other well established clinical and ECG predictors.

Global longitudinal strain vs. left ventricular ejection fraction and wall motion score index

As previously described, LVEF and WMSI are important echocardiographic prognosticators, especially in patients with coronary artery disease.[3-7] However, the assessment of LVEF and WMSI has several limitations. The measurement of LVEF with 2D echocardiography is based on geometrical assumptions used to calculate LV volumes. Although biplane Simpson's method is the most accurate 2D measurement to calculate LVEF, the presence of wall motion abnormalities or distorted LV geometry, may reduce the accuracy of this method to estimate LV systolic function and increase the intra- and inter-observer variability. Moreover, the assessment of WMSI is based on visual assessment and requires high expertise.

At present, speckle tracking echocardiography is emerging as novel technique to allow the assessment of LV mechanics through the quantification of active myocardial deformation.[8-10] Cumulative data show that, unlike LVEF and WMSI, the

assessment of LV mechanics with 2D speckle tracking strain imaging is feasible and reproducible, does not rely on geometric assumptions and is independent of LV geometry.[8-10] In particular, the assessment of LV GLS with 2D speckle tracking echocardiography has shown to be an accurate marker of LV function.[22, 25]

Stanton et al.[13] reported in a retrospective analysis of 546 unselected patients that LV GLS assessed with 2D speckle tracking echocardiography had incremental value over LVEF and WMSI for the prediction of outcome. Furthermore, the authors showed that LV GLS assessment was more reproducible as compared to LVEF assessment.[13] These findings were also confirmed in subsequent series of heart failure patients.[14, 26]

Thus far, the largest series reporting the prognostic value of GLS included 603 patients with acute myocardial infarction,[27] 697 patients with ST-segment elevation acute myocardial infarction treated with primary coronary intervention[11] and 546 unselected patients clinically referred for echocardiography (34% had prior myocardial infarction and 17% had prior coronary revascularization.[13] The present patient population is unique as it includes a homogeneous population with chronic ischemic heart disease and far larger (n=1060) compared with previous series. Furthermore, the current study provides further insight into the prognostic value of LV GLS in patients with chronic ischemic heart disease. In this group of patients, assessment of LV systolic function may be challenged by the presence of wall motion abnormalities and highly abnormal LV geometry. Therefore, LV GLS may be a more appropriate measure of LV systolic function by direct evaluation of the myocardial contractile properties. Particularly, this study investigated the prognostic value of LV GLS in 1060 patients extending previous results. LV GLS similarly to LVEF and WMSI was more preserved in survivor patients. However, among echocardiographic parameters, GLS was independently related to all-cause mortality (hazard ratio per 5% increase, 1.69, 95% CI 1.33-2.15; p<0.001) and combined end point (all-cause mortality and heart failure hospitalization) (1.64, 95% CI 1.32-2.04; p<0.001).

Global longitudinal strain and long-term outcome

Prognosis of patients with coronary artery disease is influenced by several clinical parameters.[2, 17] Similarly to previous series, the present study showed that age, diabetes, hemoglobin levels and renal function (assessed as GFR) were significantly and independently related to all-cause mortality in patients with chronic ischemic cardiomyopathy.[2, 17] More importantly, the present study demonstrated the superior prognostic value of LV GLS over these clinical well established predictors of mortality. Furthermore, LV GLS provided significant incremental value over the clinical inde-

pendent predictors of long-term outcome. Particularly, in the present evaluation the patient population was dichotomized based on the median value of LV GLS (-11.5%) showing a significantly better long-term survival for patients with less impaired LV GLS.

This finding underscores that LV GLS assessed with 2D speckle tracking echocardiography may be used as novel index of LV longitudinal function and also as strong predictor of all-cause mortality in patients with chronic ischemic cardiomyopathy.[22, 25]

Study limitations

Although the present evaluation was retrospective in design, this is the largest population cohort in which LV GLS was analyzed. An additional limitation to the present study is that radial and circumferential strains were not explored. However, it has recently been proven that longitudinal deformation may be a more sensitive marker of cardiac function which better exploring the endocardial function as compared to radial or circumferential strain.[28, 29] This issue is particularly relevant in chronic ischemic patients.[29]

The multivariate models presented are non-nested models and therefore, the comparison between the likelihoods may not be appropriate. Therefore, we could not demonstrate that GLS provided superior incremental prognostic value over LVEF and WMSI. However, the models including GLS had the lowest -2log likelihood and the highest Harrell's C statistic suggesting that GLS may be a valuable method to risk stratifiy patients with chronic ischemic heart disease. Other echocardiographic parameters related to long-term outcome of patients with chronic ischemic heart disease such as left atrial volume, mitral regurgitation and diastolic function were not evaluated.

CONCLUSION

The assessment of LV GLS with speckle tracking echocardiography is significantly related to long-term outcome in patients with chronic ischemic cardiomyopathy. Particularly, LV GLS was independently related to all-cause mortality and provided incremental prognostic value over other well established clinical and ECG predictors.

Clinical perspective

In patients with chronic ischemic cardiomyopathy, left ventricular (LV) ejection fraction (EF) and wall motion score index (WMSI) are well established predictors of long-term outcome. However, both LVEF and WMSI have some limitations related to reproducibility, geometric assumption and expertise. Recently, two-dimensional (2D) speckle tracking echocardiography permit the assessment of active myocardial deformation in radial, circumferential and longitudinal directions. The measurement of LV global longitudinal strain (GLS), which is a measure of the active shortening of the LV in the longitudinal direction, is more reproducible than LVEF and WMSI and does not rely on geometrical assumptions. The present study showed that the assessment of LV GLS with 2D speckle tracking echocardiography is significantly related to long-term outcome in patients with chronic ischemic cardiomyopathy. Moreover, LV GLS was independently related to all-cause mortality and provided incremental prognostic valve over other well established clinical and ECG predictors. Therefore, these findings underscore that LV GLS assessed with 2D speckle tracking echocardiography may be used as novel index of LV longitudinal function and also as predictor of all-cause mortality in patients with chronic ischemic cardiomyopathy.

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