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ORIGINAL RESEARCH ARTICLE

Global longitudinal strain corrected by RR interval is a superior predictor of all-cause mortality in patients with systolic heart failure and atrial fibrillation

Daniel Modin[1]*, Morten Sengeløv[1], Peter Godsk Jørgensen[1,2], Niels Eske Bruun[1,3], Flemming Javier Olsen[1], Maria Dons[1], Thomas Fritz Hansen[1], Jan Skov Jensen[1,2] and Tor Biering-Sørensen[1,2,4]

[1]*Department of Cardiology, Herlev & Gentofte Hospital, University of Copenhagen, Niels Andersensvej 65, Post 835DK-2900, Copenhagen, Denmark;* [2]*Institute of Clinical Medicine, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark;* [3]*Clinical Institute, Aalborg University, Aalborg, Denmark;* [4]*Cardiovascular Medicine Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*

Abstract

Aims Quantification of systolic function in patients with atrial fibrillation (AF) is challenging. A novel approach, based on RR interval correction, to counteract the varying heart cycle lengths in AF has recently been proposed. Whether this method is superior in patients with systolic heart failure (HFrEF) with AF remains unknown. This study investigates the prognostic value of RR interval-corrected peak global longitudinal strain {GLSc = GLS/[RR^(1/2)]} in relation to all-cause mortality in HFrEF patients displaying AF during echocardiographic examination.

Methods and results Echocardiograms from 151 patients with HFrEF and AF during examination were analysed offline. Peak global longitudinal strain (GLS) was averaged from 18 myocardial segments obtained from three apical views. GLS was indexed with the square root of the RR interval {GLSc = GLS/[RR^(1/2)]}. Endpoint was all-cause mortality. During a median follow-up of 2.7 years, 40 patients (26.5%) died. Neither uncorrected GLS (P = 0.056) nor left ventricular ejection fraction (P = 0.053) was significantly associated with all-cause mortality. After RR^(1/2) indexation, GLSc became a significant predictor of all-cause mortality (hazard ratio 1.16, 95% confidence interval 1.02–1.22, P = 0.014, per %/s^(1/2) decrease). GLSc remained an independent predictor of mortality after multivariable adjustment (age, sex, mean heart rate, mean arterial blood pressure, left atrial volume index, and E/e′) (hazard ratio 1.17, 95% confidence interval 1.05–1.31, P = 0.005 per %/s^(1/2) decrease).

Conclusions Decreasing {GLSc = GLS/[RR^(1/2)]}, but not uncorrected GLS nor left ventricular ejection fraction, was significantly associated with increased risk of all-cause mortality in HFrEF patients with AF and remained an independent predictor after multivariable adjustment.

Keywords Global longitudinal strain; Heart failure with reduced ejection fraction; Atrial fibrillation; Speckle tracking; Risk stratification

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**Correspondence to: Daniel Modin, Department of Cardiology, Herlev & Gentofte Hospital, University of Copenhagen, Niels Andersensvej 65, Post 835, DK-2900 Copenhagen, Denmark. Tel: +45 4182 8993; Fax: +45 3977 7381. Email: danielmodin@live.dk*

Introduction

Echocardiographic quantification of left ventricular (LV) systolic function in heart failure (HF) patients has improved survival rates as a result of better and intensified medical treatment.[1,2] It has previously been shown that atrial fibrillation (AF) modifies and incapacitates the predictive value of several echocardiographic parameters normally used to asses LV function.[3] New methods for echocardiographic risk stratification in patients displaying AF at examination are therefore needed.

Quantification of LV function presents a challenge in AF patients due to a variety of factors: elevated heart rate, greatly increased beat-to-beat duration variability (RR interval), and absence of atrial contraction (usually measured as late diastolic velocities: A, a′). All significantly disrupt routine echocardiographic usability. These difficulties often result in exclusion of AF patients from echocardiographic studies or

in a limited inclusion of patients only displaying low RR variability.

Myocardial strain parameters have shown proficiency in predicting outcome and quantifying LV function in several patient groups, a few of these being ischaemic heart disease,[4] HF with reduced ejection fraction (HFrEF),[3] and HF with preserved ejection fraction.[5] Our group has recently demonstrated peak global longitudinal strain (GLS) to be a superior prognosticator of all-cause mortality in patients with HFrEF.[3] Despite these results, no prognostic value of GLS was found in HFrEF patients displaying AF at examination. This calls for further research into markers of significant prognostic value in patients with AF.

The widely accepted method to overcome the varying RR interval observed in AF is presently to obtain echocardiographic imaging and parameters from preferentially 10–15 consecutive heart cycles, with subsequent averaging of values to obtain parameters somewhat representative of true LV function.[6] This is highly impractical in a busy clinical setting and may therefore result in poor echocardiographic assessment of patients displaying AF. Recently, a novel method to counteract the varying cycle length observed in AF has been proposed.[7] This strategy is based on correction of the strain parameters by the square root of the particular RR interval in which the measurements were made, a strategy also employed in QT-interval correction (Bazett's formula). Correction by RR interval has been suggested as a superior method compared with averaging of several heart cycles.[7,8] The same method has been demonstrated to be successful in predicting outcome in patients with AF through correction of GLS by the square root of RR.[9]

In light of presented information, this study evaluates the predictive value of GLS, GLSc, peak global circumferential strain (GCS), and corrected GCS (GCSc) in HFrEF patients with AF during examination in comparison with conventional echocardiographic parameters.

Methods

Data

The Department of Cardiology, Herlev & Gentofte Hospital, University of Copenhagen, conducts routine echocardiographic assessments according to a standardized protocol.[3,7] Results have been stored in a local hard drive since 2005.

Study population

This retrospective study included echocardiographic examinations from 151 HFrEF patients with AF. The identification of the HFrEF population for this study has been described in detail elsewhere.[3] Briefly, patients were selected from a population of non-acute HFrEF patients referred to the HF clinic at Gentofte University Hospital from 2005 to 2013.[3] Only patients with an LV ejection fraction (LVEF) $<45\%$ were considered. Only patients who presented with AF during echocardiographic examination and a frame rate adequate for strain analysis ($\geq$45 frames per second) were considered. Baseline clinical characteristics were retrieved from the HFrEF database and were originally recorded by the clinic at the first visit. All patients had been diagnosed with HFrEF by an experienced clinician. Mortality status information was retrieved from the Danish National Registry of Mortality at follow-up, and follow-up was 100%. Ischaemic cardiomyopathy was defined as patients having a history of myocardial infarction and/or having undergone percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery.

Echocardiography

All echocardiographic assessments were obtained through either Vivid 7 or 9 echocardiographic machines (GE Healthcare, Horten, Norway) and stored in a GE Healthcare Image Vault. Analysis of echocardiographic data was subsequently performed offline by a single investigator blinded to all patient data by use of Echopac version 12 (GE Healthcare).

Conventional

Left ventricular ejection fraction was calculated using the modified Simpson biplane method from the apical four-chamber and two-chamber views.[10] Therefore, LVEF calculation was derived from two cardiac cycles. LV end-diastolic dimensions were measured in the parasternal long-axis view at the tip of the mitral valve leaflets. Parameters measured include interventricular septal thickness, LV posterior wall dimensions, and LV internal dimensions.[10]

LV mass was estimated using the Devereux formula.[11] Furthermore, LV mass was divided by body surface area to obtain the LV mass index. Estimation of body surface area was obtained through use of the Du Bois formula.[12] Left atrial volume was obtained by the biplane area length method and left atrial volume index (LAVI) by division with body surface area.[10]

The tricuspid annular plane systolic excursion (TAPSE) was measured through M-mode echocardiography in the apical four-chamber view, placing the M-mode cursor on the lateral tricuspid annulus.

Pulsed-wave Doppler analysis in the apical four-chamber view was used to evaluate diastolic mitral inflow patterns and measure peak early transmitral inflow velocity (E) and deceleration time of the early diastolic inflow. Pulsed-wave tissue Doppler imaging analysis with region of interest (ROI) positioned in the lateral and septal part of the mitral annulus

in the apical four-chamber view was used to determine peak longitudinal tissue velocity during early diastolic filling (e′). A mean e′ between the septal and lateral velocity was calculated, and E was indexed by e′ to yield a representation of filling pressure during diastole (E/e′).

Speckle tracking echocardiography

Longitudinal speckle tracking analysis in a single heart cycle was performed in the apical four-chamber view, apical two-chamber view, and apical long-axis view; and GLS was averaged from a total of 18 myocardial segments. Therefore, GLS was derived from three heart cycles, one from each view. GCS was averaged from six myocardial segments obtained from the parasternal short-axis view at mid-ventricular level. For both longitudinal and circumferential analyses, the endocardial border was manually defined by point and click by the investigator at end-systole, with subsequent automatic detection of the epicardial border; hence, the final ROI was generated as the result of a semi-automated process. Before acceptance of ROI, the investigator visually inspected each myocardial segment in all views for acceptable tracking of speckles and either accepted or rejected each segment based on this assessment. If segmental tracking was deemed inadequate, attempts to correct the ROI in this particular segment were made by the investigator by manual adjustment. In case of persistent unacceptable tracking, the particular segment was excluded. In case of shadowing of a myocardial segment by an artefact, the segment was excluded. Furthermore, aortic valve closure was visually assessed by the investigator.

In order to adjust for the varying heart cycle interval observed in AF rhythm, correction by the square root of the RR interval was used to index values of both GLS and GCS, hereby obtaining GLSc {GLSc = GLS/[RR^(1/2)]} and GCSc {GCSc = GCS/[RR^(1/2)]}.

Statistical analysis

All statistical analyses were performed using STATA version 13.0 on Mac OS. Statistical significance was defined as $P < 0.05$. Continuous Gaussian distributed variables were compared using two-tailed Student's *t*-test, while categorical variables were compared through use of the χ^2 test. In case of mean comparison between more than two groups, one-way ANOVA with subsequent post hoc analysis (Scheffe) was used. To analyse trend, linear regressions of means were performed. Survival curves were constructed through use of the Kaplan–Meier method. Survival analysis was conducted through both univariable and multivariable Cox regressions. The variables chosen for the multivariable analysis were age, sex, heart rate, mean arterial pressure, LAVI, and E/e′. In order to assess the prognostic strength of examined parameters, Harrell's *C*-statistics were calculated for each Cox regression model.

Results

Predictors of all-cause mortality in systolic heart failure patients with atrial fibrillation

During a median follow-up of 2.7 years, 40 patients (26.5%) died. No clinical baseline characteristics were significantly different between patients alive and patients dead at follow-up. With regard to echocardiographic parameters, patients who died had significantly larger LAVI, significantly lower TAPSE, and significantly lower values of GLSc, GCSc, and GCS. Among parameters not reaching statistical significance at baseline were LVEF and GLS (*Table 1*).

Mean RR interval was 0.792 s (SD: 0.19 s), corresponding to a mean heart rate of 80 b.p.m. (SD: 20 b.p.m.), and no significant difference in neither mean heart rate nor RR interval between patients alive at follow-up and patients dead at follow-up was found.

Stratification of the population by tertiles of GLSc was performed. Male gender was more frequent with decreasing tertile of GLSc (*Table 2*). With regard to echocardiographic parameters, decreasing tertile of GLSc was significantly associated with decreasing value of LVEF, increasing value of LV internal diameter at end-diastole, increasing LV mass index, shortened deceleration time, and lower TAPSE (*Table 2*).

Univariable Cox regression was carried out with parameters that displayed statistical significance at baseline (*Table 3*). Significant univariable predictors included GLSc, GCSc and GCS, LAVI, and TAPSE. In multivariable models (age, sex, mean arterial pressure, heart rate, LAVI, and E/e′), GLSc, GCSc, and GCS remained significant predictors of mortality [GLSc: hazard ratio (HR) 1.17, 95% confidence interval (CI) 1.05–1.31, $P = 0.005$, per $\%/s^{(1/2)}$ decrease; GCSc: HR 1.19, 95% CI 1.06–1.33, $P = 0.003$, per $\%/s^{(1/2)}$ decrease; and GCS: HR 1.18, 95% CI 1.04–1.33, $P = 0.011$, per % decrease] (*Table 3*). Neither LAVI nor TAPSE remained significant predictors in the multivariable analysis.

Each instance of (RR)^(1/2) correction provided an increase in prognostic value as reflected in increased *C*-statistics for GLSc and GCSc compared with those for GLS and GCS. Both GCSc and GCS remained significant after multivariable adjustment, but GCSc displayed markedly higher *C*-statistics. GLSc displayed higher *C*-statistics than any other parameters in the multivariable model (*Table 3*).

Cox regression with the population stratified into tertiles of GLSc was carried out. In univariable analysis of GLSc tertiles, patients in the lowest tertile displayed a three times higher risk of dying than did the patients in the highest tertile (first tertile vs. third tertile, HR 3.00, 95% CI 1.37–6.60,

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Table 1 Clinical and echocardiographic characteristics

	All patients	Alive at follow-up	Dead at follow-up	*P*-value
Clinical characteristics				
n	151	111	40	
Age (years)	70.5 (9.2)	69.7 (9.2)	72.5 (8.9)	0.10
Male	119 (78.8%)	87 (78.4%)	32 (80.0%)	0.83
Heart rate (b.p.m.)	80.3 (20.4)	80.4 (18.8)	80.0 (24.4)	0.91
BMI (kg/m^2)	26.7 (5.1)	27.0 (5.0)	25.8 (5.5)	0.19
Diabetes mellitus	14 (9.2%)	12 (10.8%)	2 (5.0%)	0.28
MAP (mmHg)	93.4 (14.2)	93.5 (14.9)	93.2 (12.4)	0.93
Ischaemic cardiomyopathy	65 (43%)	50 (45.0%)	15 (37.5%)	0.41
Total cholesterol (mmol/L)	4.5 (1.0)	4.5 (1.0)	4.4 (1.1)	0.50
Angina pectoris	27 (18)	18 (16.2%)	9 (22.5%)	0.37
CABG	31 (21%)	26 (23.4%)	5 (12.5%)	0.14
Beta-blockers	104 (69%)	74 (66.7%)	30 (75.0%)	0.33
RAS blockade	125 (83%)	92 (82.9%)	33 (82.5%)	0.96
Diuretics	80 (53%)	60 (54.1%)	20 (50.0%)	0.66
Antiarrhythmics	8 (5.0%)	6 (5.4%)	2 (5.0%)	0.92
Calcium channel blocker	2 (1.0%)	2 (1.8%)	0 (0.0%)	0.39
Anticoagulants	2 (1.3%)	2 (1.8%)	0 (0.0%)	0.39
Spironolactone	17 (11.0%)	12 (10.8%)	5 (12.5%)	0.77
Echocardiography				
LVEF (%)	26.2 (9.4)	27.1 (8.6)	23.7 (11.0)	0.053
RR interval (s)	0.792 (0.190)	0.890 (0.180)	0.810 (0.220)	0.47
LVIDd (cm)	5.7 (0.9)	5.6 (0.8)	5.7 (1.1)	0.50
LVMI (g/m^2)	117.5 (32.4)	116.4 (33.1)	120.3 (30.6)	0.52
LAVI (mL/m^2)	42.1 (19.0)	40.2 (15.3)	47.5 (26.0)	0.035
E (m/s)	0.97 (0.300)	0.97 (0.306)	0.96 (0.281)	0.93
e′ (m/s)	0.086 (0.026)	0.087 (0.027)	0.082 (0.021)	0.32
E/e′	11.9 (5.3)	11.8 (5.39)	12.4 (5.00)	0.57
DT (ms)	159 (61)	160 (54)	159 (75)	0.93
TAPSE (cm)	1.6 (0.5)	1.6 (0.5)	1.4 (0.5)	0.016
GLS (%)	−10.1 (3.6)	−10.5 (3.4)	−9.2 (3.9)	0.056
GCS (%)	−9.3 (3.5)	−9.7 (3.6)	−8.1 (2.9)	0.022
GLSc (%/s$^{(1/2)}$)	−11.4 (3.9)	−11.8 (3.7)	−10.2 (4.3)	0.022
GCSc (%/s$^{(1/2)}$)	−10.5 (4.2)	−11.1 (4.2)	−8.9 (3.7)	0.007

BMI, body mass index; CABG, coronary artery bypass grafting; DT, E-wave deceleration time; GCS, global circumferential strain; GCSc, RR-corrected global circumferential strain {GCSc = GCS/[RR ^ (1/2)]}; GLS, global longitudinal strain; GLSc, RR-corrected global longitudinal strain {GLSc = GLS/[RR ^ (1/2)]}; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diameter at end-diastole; LVMI, left ventricular mass index; MAP, mean arterial pressure; RAS, renin–angiotensin system; TAPSE, tricuspid annular plane systolic excursion.

P = 0.006) (*Figure 1*). After multivariable adjustment, the risk was approximately four times higher and remained statistically significant (first tertile vs. third tertile, HR 3.8 95% CI 1.40–10.31, *P* = 0.009).

Discussion

Quantification of LV function during AF rhythm presents a significant challenge due to a variety of factors such as a rapid heart rate, a greatly increased beat-to-beat duration variability (RR interval), and absence of the late diastolic velocity wave (A, a′). These factors all partly disrupt the prognostic efficacy of conventional echocardiographic parameters. These phenomena are partly to blame for the relatively low amount of knowledge accumulated in the scientific community with regard to echocardiographic assessment of LV function in AF patients. We propose that strain corrected by RR interval {GLSc = GLS/[RR^(1/2)]} is a practical and superior strategy to counterbalance the changing haemodynamics observed in AF. This proposal is based on our findings tying decreasing values of GLSc to a significantly increased risk of death in HFrEF patients displaying AF at echocardiographic examination.

Varying cycle length observed in atrial fibrillation

Counteraction of the cycle length variability displayed in AF rhythm has previously been attempted through averaging of echocardiographic parameters from multiple consecutive heart cycles, preferably 5–15.[13,14] This strategy not only is cumbersome and time-consuming but also may run a risk of negligence in a busy clinical setting due to its extensive nature. As a response to this extensive nature of cardiac cycle averaging, the index beat method has been proposed as an alternative method and has been demonstrated to be superior to cardiac cycle averaging despite varying RR intervals.[7,8]

The index beat method is dependent on the pre-preceding

Table 2 Clinical and echocardiographic characteristics by tertiles of GLSc

	Lowest tertile GLSc < 9.5%/s$^{(1/2)}$	Middle tertile GLSc = 9.5–12.8%/s$^{(1/2)}$	Highest tertile GLSc > 12.8%/s$^{(1/2)}$	*P*-value for trend
Clinical characteristics				
n	50	50	51	
Age (years)	69.7 (8.5)	71.5 (8.5)	70.1 (10.4)	0.82
Male	46 (92%)	39 (78%)	34 (67%)	0.002
Heart rate (b.p.m.)	82.1 (24.0)	79.2 (22.0)	79.5 (15.0)	0.52
BMI (kg/m^2)	27.4 (5.5)	26.8 (4.6)	25.9 (5.1)	0.14
Diabetes mellitus	7 (14%)	6 (12%)	1 (2%)	0.08
MAP (mmHg)	92.6 (13.3)	93.5 (13.4)	94.0 (16.1)	0.62
Ischaemic cardiomyopathy	22 (44%)	24 (48%)	19 (37%)	0.49
Total cholesterol (mmol/L)	4.4 (1.1)	4.6 (1.0)	4.5 (1.0)	0.76
Angina pectoris	8 (16%)	10 (20%)	9 (18%)	0.83
CABG	11 (22%)	12 (24%)	8 (16%)	0.43
Beta-blockers	32 (64%)	35 (70%)	37 (73%)	0.36
RAS blockade	44 (88%)	37 (74%)	44 (86%)	0.83
Diuretics	25 (50%)	25 (50%)	30 (59%)	0.38
Antiarrhythmics	3 (6%)	2 (4%)	3 (6%)	0.98
Calcium channel blockers	1 (2%)	0 (0%)	1 (2%)	0.99
Anticoagulants	1 (2%)	1 (2%)	0 (0%)	0.38
Spironolactone	9 (18%)	4 (8%)	4 (8%)	0.11
Echocardiography				
n	50	50	51	
LVEF (%)	18.6 (7.1)	26.1 (7.5)	33.6 (6.8)	<0.001
RR interval (s)	0.792 (0.211)	0.813 (0.203)	0.781 (0.150)	0.87
LVIDd (cm)	6.2 (0.9)	5.6 (0.75)	5.2 (0.8)	<0.001
LVMI (g/m^2)	125 (34)	122 (29)	105 (31.0)	0.001
LAVI (mL/m^2)	46.6 (17.7)	40.0 (12.6)	40.1 (24.2)	0.08
E (m/s)	0.98 (0.25)	0.95 (0.29)	0.97 (0.36)	0.87
e′ (m/s)	0.080 (0.021)	0.091 (0.032)	0.100 (0.031)	0.035
E/e′	12.8 (5.3)	12.3 (6.3)	10.5 (3.8)	0.046
DT (ms)	137 (50)	160 (68)	182 (55)	<0.001
TAPSE (cm)	1.5 (0.4)	1.5 (0.5)	1.8 (0.5)	0.002
GLS (%)	−6.5 (1.9)	−10.0 (1.5)	−13.8 (2.2)	<0.001
GCS (%)	−7.9 (3.5)	−9.5 (3.0)	−10.5 (3.6)	<0.001
GCSc (%/s$^{(1/2)}$)	−9.0 (3.7)	−10.8 (3.8)	−11.9 (4.5)	0.001

BMI, body mass index; CABG, coronary artery bypass grafting; DT, E-wave deceleration time; GCS, global circumferential strain; GCSc, RR-corrected global circumferential strain {GCSc = GCS/[RR^(1/2)]}; GLS, global longitudinal strain; GLSc, RR- corrected global longitudinal strain {GLSc = GLS/[RR^(1/2)]}; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diameter end-diastole; LVMI, left ventricular mass index; MAP, mean arterial pressure; RAS, renin–angiotensin system; TAPSE, tricuspid annular plane systolic excursion.

Table 3 Cox regression models

	Hazard ratio	*C*-statistics	*P*-value
Univariable			
LAVI (per increasing mL/m^2)	HR 1.02, 95% CI 1.00–1.03	0.545	0.036
TAPSE (per increasing cm)	HR 0.43, 95% CI 0.20–0.89	0.634	0.023
GCS (per decreasing %)	HR 1.14, 95% CI 1.03–1.27,	0.636	0.015
GLSc (per decreasing %/s$^{(1/2)}$)	HR 1.12, 95% CI 1.02–1.22	0.636	0.014
GCSc (per decreasing %/s$^{(1/2)}$)	HR 1.14, 95% CI 1.04–1.26	0.645	0.006
Multivariable (age, sex, MAP, and heart rate)			
LAVI (per increasing mL/m^2)	HR 1.01, 95% CI 1.00–1.03	0.601	0.081
TAPSE (per increasing cm)	HR 0.46, 95% CI 0.21–0.98	0.642	0.045
GCS (per decreasing %)	HR 1.18, 95% CI 1.04–1.33	0.659	0.011
GLSc (per decreasing %/s$^{(1/2)}$)	HR 1.17, 95% CI 1.05–1.31	0.681	0.005
GCSc (per decreasing %/s$^{(1/2)}$)	HR 1.19, 95% CI 1.06–1.33	0.671	0.003
Multivariable (age, sex, MAP, heart rate, LAVI, and E/e′)			
TAPSE (per increasing cm)	HR 0.46, 95% CI 0.20–1.06	0.625	0.068
GCS (per decreasing %)	HR 1.18, 95% CI 1.04–1.33	0.659	0.011
GLSc (per decreasing %/s$^{(1/2)}$)	HR 1.17, 95% CI 1.05–1.31	0.681	0.005
GCSc (per decreasing %/s$^{(1/2)}$)	HR 1.19, 95% CI 1.06–1.33	0.671	0.003

CI, confidence interval; GCS, global circumferential strain; GCSc, RR-corrected global circumferential strain {GCSc = GCS/[RR^(1/2)]}; GLSc, RR-corrected global longitudinal strain {GLSc = GLS/[RR^(1/2)]}; LAVI, left atrial volume index; MAP, mean arterial pressure; TAPSE, tricuspid annular plane systolic excursion.

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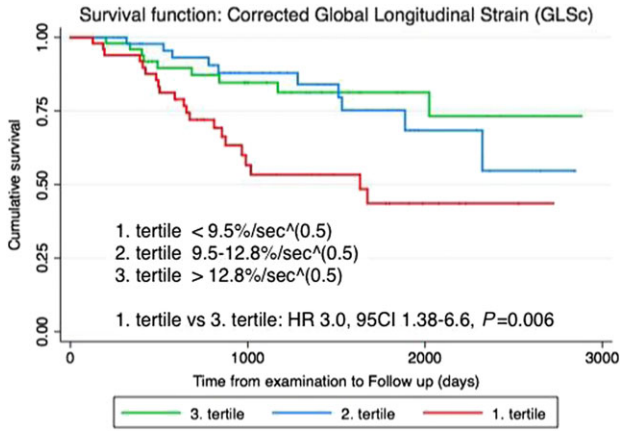
Figure 1 The curves display the cumulative survival of the population stratified into tertiles of corrected global longitudinal strain (GLSc) as a function of time from examination. The red curve depicts the cumulative survival of patients in the lowest tertile of GLSc. The green curve depicts the cumulative survival of patients in the highest tertile of GLSc. The blue curve depicts the cumulative survival of patients in the middle tertile of GLSc. CI, confidence interval; HR, hazard ratio.



RR interval and the preceding RR interval having a ratio of 1 (RR1/RR2 = 1). Obtainment of an RR1/RR2 = 1 sequence of beats in any finite examination time is dependent on chance. Hence, this calls for more research into a new and more applicable method to correct for the difficulties faced in obtaining valid echocardiographic parameters from AF patients. Since neither cycle averaging nor index beat correction can be applied in larger population studies with only one or two heart cycles on record, and both are heavily dependent on chance in addition to being time-consuming, a novel method of cycle length indexation is needed.

Global longitudinal strain obtained by the index beat method has been demonstrated as a significant independent prognosticator in patients with AF.[15] Our study shows that decreasing values of GLSc, thus values obtained from only a single cycle, were significantly associated with all-cause mortality in patients with HFrEF displaying AF rhythm at examination. These results must be viewed in relation to the finding that neither LVEF nor GLS was significantly different between patients who died during follow-up and patients who were alive. Indexation of GLS by RR made GLSc a significant predictor at baseline, and it remained so in multivariable models. Furthermore, GLSc displayed higher *C*-statistics than did all other echocardiographic parameters in both univariable and multivariable models. In addition to GLSc, we found that GCS and GCS indexed by RR interval (GCSc) were also significant predictors of death, in both univariable and multivariable models. It must, however, be noted that GCS, and therefore also GCSc, was only measured in a single echocardiographic view in this study, the parasternal short-axis view at the mid-ventricular level. It does, however, provide indication that more research into the prognostic value of GCS and GCSc with regard to prediction of outcome in HFrEF patients with AF is warranted.

Justification of RR interval indexation is further solidified by results previously reported that GLSc correlated well when obtained during sinus rhythm and AF measured in the same patient, as opposed to uncorrected GLS and LVEF.[7] It has also recently been demonstrated that only GLSc, neither uncorrected GLS nor LVEF, remained an independent predictor after multivariate adjustment in AF patients without known HF, when a composite endpoint was defined as incidental HF, stroke, myocardial infarction, and all-cause mortality.[9]

Taking the results of our study into consideration, RR interval correction appears to emerge as a valid strategy to counteract the varying haemodynamics observed in AF rhythm.

Atrial fibrillation and heart failure

Research into methods of counteracting the haemodynamics alterations from beat to beat in AF only becomes more important when the frequent coexistence of AF and HF is taken into consideration.[16,17] Effective quantification of LV function significantly improves patient risk status and survival mainly through intensified medical treatment and intervention.[1,2] Our findings provide new insights into the prognostic value of strain imaging indexed by the square root of the RR interval in HFrEF patients with AF. These results therefore contribute to better risk stratification of HFrEF patients with AF.

Limitations

Some limitations to the results of this study must be acknowledged. Strain analysis was conducted offline, and all echocardiographic examinations were obtained in a routine clinical setting—this increases the likelihood that suboptimal acoustic circumstances were accepted during examination. In our view, potential inclusion of suboptimal echocardiographic examinations would only serve to weaken any found associations and hence reinforces the significance of our results. In addition, a risk of selection bias must also be acknowledged. Furthermore, only two-dimensional (2D) imaging was available in echocardiograms included in this study. Three-dimensional (3D) speckle tracking echocardiography (3DSTE) is emerging as a potentially superior method of LV quantification.[18] Both longitudinal strain and circumferential strain parameters derived from 3DSTE have been shown to be different and more accurate than strain parameters derived from 2D speckle tracking (2DSTE).[18] 3DSTE has also been shown to be a superior method of quantifying LV twist and torsion compared with 2DSTE.[19] 2DSTE can display inferior tracking because of speckles moving out of the imaging plane

in the *z*-axis direction.[18,20] This could potentially cause inadequate and incorrect measurement of 2DSTE strain parameters. 3DSTE does not suffer from the issue of speckles moving out of the imaging plane because of tracking of the entire left ventricle. However, 3DSTE requires frame stitching of multiple consecutive cardiac cycles,[20] something that is infeasible in AF rhythm because of the highly irregular RR interval displayed by patients in AF rhythm. Also, 3DSTE techniques display lower frame rates than do 2DSTE techniques, and given that AF patients display consistently higher heart rates, the low frame is an issue. Hence, it remains to be assessed whether uncorrected 3DSTE GLS is prognostic in HFrEF patients displaying AF during examination. However, if the technical limitations regarding 3DSTE can be overcome, evaluation of the prognostic value of 3DSTE strain parameters in HFrEF patients displaying AF rhythm would be of great interest because of previously mentioned advantages of 3DSTE compared with 2DSTE. Lastly, only one heart cycle in each view was available for analysis in the included echocardiograms. Therefore, we were not able to determine RR variability or the RR1/RR2 ratio surrounding the particularly cycle on record in each view. As a result, LVEF was derived from two cardiac cycles (apical four chamber and apical two chamber), and GLS was derived from three cycles (apical four chamber, apical two chamber, and apical long axis). Due to lack of multiple cardiac cycles in each view, we were not able to compare the prognostic value of GLSc with that of GLS obtained using the index beat method. By extension, future studies are needed in order to validate our suggested approach against the index beat method.

Conclusions

Decreasing GLSc {GLSc = GLS/[RR^(1/2)]}, but not GLS or LVEF, was significantly associated with increased risk of all-cause mortality in HFrEF patients with AF and remained an independent predictor after multivariable adjustment.

Conflict of interest

None declared.

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