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SHORT COMMUNICATION

A global longitudinal strain cut-off value to predict adverse outcomes in individuals with a normal ejection fraction

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Abstract

Aims Global longitudinal strain (GLS) has become an alternative to left ventricular ejection fraction (LVEF) to determine systolic function of the heart. The absence of cut-off values is one of the limitations preventing full clinical implementation. The aim of this study is to determine a cut-off value of GLS for an increased risk of adverse events in individuals with a normal LVEF.

Methods and results Echocardiographic images of 502 subjects (52% female, mean age 48 ± 15) with an LVEF ≥ 55% were analysed using speckle tracking-based GLS. The primary endpoint was cardiovascular death or cardiac hospitalization. The analysis of Cox models with splines was performed to visualize the effect of GLS on outcome. A cut-off value was suggested by determining the optimal specificity and sensitivity. The median GLS was −22.2% (inter-quartile range −20.0 to −24.9%). In total, 35 subjects (7%) had a cardiac hospitalization and/or died because of cardiovascular disease during a follow-up of 40 (5–80) months. There was a linear correlation between the risk for adverse events and GLS value. Subjects with a normal LVEF and a GLS between −22.9% and −20.9% had a mildly increased risk (hazard ratio 1.01–2.0) for cardiac hospitalization or cardiovascular mortality, and the risk was doubled for subjects with a GLS of −20.9% and higher. The optimal specificity and sensitivity were determined at a GLS value of −20.0% (hazard ratio 2.49; 95% confidence interval: 1.71–3.61).

Conclusions There is a strong correlation between cardiac adverse events and GLS values in subjects with a normal LVEF. In our single-centre study, −20.0% was determined as a cut-off value to identify subjects at risk. A next step should be to integrate GLS values in a multi-parametric model.

Keywords Global longitudinal strain; Echocardiography; Healthy; Prognosis

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Background

Increasing evidence suggests that global longitudinal strain (GLS) is superior to left ventricular ejection fraction (LVEF) as a predictor of mortality and cardiac events in early cardiomyopathies.[1,2] However, the clinical utility of GLS is still hampered because of the lack of clear cut-off values for clinical decision making. The World Alliance Societies of Echocardiography Normal Values Study evaluated healthy individuals from multiple countries with the aim to describe normal values for echocardiographic measures.[3] GLS was determined in 1.882 subjects within this study, which revealed a lower limit of normal GLS of −17% and −18% in men and women, respectively. Although the range of GLS values was investigated, these values were not associated with outcome during follow-up. Therefore, the interpretation of these

normal values in relation to prognosis in individuals with normal LVEF remains unknown. Previously, we showed a worse prognosis using a predetermined GLS cut-off value of −21.5% in two independent cohorts with normal LVEF.[1,4]

Aims

The aim of this study was to determine a cut-off value of GLS that indicates increased risk of adverse outcome in individuals with a normal LVEF.

Methods

We used the dataset from our previous publication for this analysis, including 502 subjects with an LVEF ≥ 55%.[1] All subjects underwent cardiac screening including echocardiography at our outpatient clinic. None of the subjects had systolic dysfunction, although some subjects were referred for chest pain, dyspnoea, or palpitations and had cardiovascular co-morbidities.[1] None of the patients had a previous history of heart failure. Analysis of left ventricular function with speckle tracking-based GLS was performed and corrected blindly on the echocardiographic images by four independent investigators,[1] applying a dedicated software package (AutoSTRAIN, TOMTEC-ARENA*1.2, TOMTEC Imaging Systems GmbH, Unterschleißheim, Germany). The primary endpoint was cardiovascular death or cardiac hospitalization. The analysis of Cox models with splines was performed with the survival package v3.2-7 in R (R Foundation for Statistical Computing, Vienna, Austria).

Results

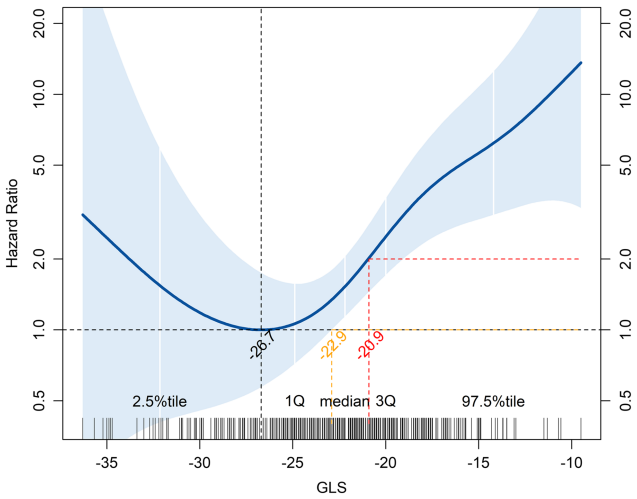
The baseline characteristics of the study population are shown in *Table 1*. The median GLS was −22.2% (inter-quartile range −20.0 to −24.9%). In total, 35 subjects (7%) had a cardiac hospitalization and/or died because of cardiovascular disease(s) during a follow-up of 40 (5–80) months.[1] Subjects with an event had a mean GLS value of −19.7 ± 4.9%, compared with −22.8 ± 4.2% in patients without event ($P < 0.001$). Twenty-five subjects were hospitalized (mean GLS −20.3 ± 4.8% vs. −22.7 ± 4.3%, $P = 0.006$), and 11 died because of cardiovascular reasons (mean GLS −17.9 ± 4.9% vs. −22.7 ± 4.3%, $P < 0.001$). The lowest risk was observed for the subjects who had a strain value of −26.7% (*Figure 1*), which was subsequently set as the reference point [hazard ratio (HR) = 1.0]. The population density and number of events were too low below −26.7% (increasing strain value) to draw any conclusions, which is reflected by the wide 95% confidence interval and non-significance of increased risk. A worse GLS value (>−26.7) was associated with an increased risk for the primary endpoint. A GLS value of −22.9% was the lowest strain value at which there was a significant increased risk compared with individuals with a GLS of −26.7% (HR 1.34; 95% confidence interval: 1.01–1.79). A hazard ratio of 2.0 was associated with a GLS of −20.9%

Table 1 Baseline characteristics and outcome of the total study population

	Study population (n = 502)
Male	242 (48)
Age (years)	46 ± 15
Body mass index (kg/m^2)	26 ± 5
Cardiovascular history	
Coronary artery disease	21 (4)
Stroke	8 (2)
CABG	3 (1)
PCI	11 (2)
Co-morbidities	
Atrial fibrillation	6 (1)
Hypertension	122 (24)
COPD	23 (5)
Hypercholesterolaemia	74 (15)
Diabetes mellitus	36 (7)
Combined endpoint	35 (7)
Cardiac hospitalization	25 (5)
Cardiovascular death	11 (2)

CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention.
Values are n (%) or mean ± standard deviation.

Figure 1 Hazard ratio plotted against global longitudinal strain (GLS) value. The lowest risk in the study population was associated with a GLS value of −26.7 (black line). The hazard ratio is expressed using this point as the reference. Patients with a GLS of −22.9 (orange line) had a significant higher risk, and patients with a value of −20.9 (red line) had a double risk for adverse events compared with subjects with a GLS value of −26.7. The blue line and range indicate the hazard ratio with the 95% confidence interval. Lines on the x-axis represent individual study subjects. Adverse events are defined as cardiovascular death and/or cardiac hospitalization.



(HR 2.02; 95% confidence interval: 1.45–2.81). The optimal specificity and sensitivity were determined at a GLS value of −20.0% (HR 2.49; 95% confidence interval: 1.71–3.61).

Conclusion

In this exploratory analysis, we determined a cut-off value for GLS, which can detect individuals with a normal LVEF who are at risk for cardiac hospitalization or cardiovascular mortality. A worse GLS was as expected associated with an increased risk of events.[2] Patients with a GLS between −22.9% and −20.9% had a mildly increased risk (HR 1.01–2.0), and the risk was doubled for patients with a GLS of −20.9% and higher with −20.0% as the optimal cut-off value in this population. Noteworthy, these values are lower than the previously reported lower limit of normal in men and women (−17% and −18%, respectively).[3] However, these previously reported values were not associated with outcome, making it difficult to compare these values from both populations. It is also not unusual in biology that values within the normal range can have prognostic implications (as is also the case for blood pressure and troponin for example).

Our study represents a single-centre effort, which gives an important insight in the prognostic value of GLS in patients with a normal LVEF. In this study, we used cardiac hospitalization or mortality as strong clinical outcome measure; however, GLS cut-off values regarding cardiac deterioration (e.g. reduction of LVEF) or heart failure development might differ. Moreover, given the single-centre design and previously reported vendor dependency, there is an urgent need for multicentre studies to determine the prognostic cut-off value(s) for GLS in individuals with a normal LVEF, as our results cannot be generalized to large populations.[5] Within future studies, additional efforts should be made to combine clinical phenotyping, cardiovascular imaging, and genetic information with GLS analysis to create a multi-parametric model in which the incremental value of GLS can be evaluated. Such model will identify subjects who are most susceptible for adverse (cardiac) events and paves the way for preventive (intervention) studies: using GLS to identify early disease, which creates a window of opportunity to initiate treatment before cardiac deterioration. Our study is a first step towards such intervention studies, which are necessary before GLS will be adopted in routine clinical practice.

Conflict of interest

G.S. is employed at TOMTEC Imaging Systems GmbH. C.K. has received research support (software and hardware) from TOMTEC Imaging Systems.

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