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Two-dimensional global longitudinal strain is superior to left ventricular ejection fraction in prediction of outcome in patients with left-sided infective endocarditis

Trine Kiilerich Lauridsen [a,*,1], Christina Alhede [a,1], Anna Lisa Crowley [b,1], Joseph Kisslo [b,1], Lars L. Sørensen [a,1], Thomas Fritz Hansen [a,1], Niels Risum [c,1], Carsten Toftager Larsen [d,1], Christian Hassager [c,1], Peter Søgaard [e,1], Anders Dahl [a,1], Niels Eske Bruun [a,f,1]

[a] Department of Cardiology, Herlev and Gentofte University Hospital, Denmark
[b] Department of Cardiology, Duke University Medical Center, North, Carolina, US
[c] The Heart Centre, Rigshospitalet, Denmark
[d] Department of Cardiology, Roskilde University Hospital, Denmark
[e] Department of Cardiology, Aalborg University Hospital, Denmark
[f] Clinical Institute, Aalborg University Hospital, Denmark

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Background: Impaired cardiac function is the main predictor of poor outcome in infective endocarditis (IE). Global longitudinal strain (GLS) derived from two-dimensional strain echocardiography has proven superior in prediction of long-term outcome as compared to left ventricular ejection fraction (LVEF) in valvular disease and heart failure in general. Whether measurements of cardiac deformation can predict survival in patients with IE has not previously been investigated.

Methods: The study included consecutive patients with Duke definite IE who underwent transthoracic and transesophageal echocardiography within 7 days. Clinical and echocardiographic markers associated with 1-year survival were identified using a Cox-proportional hazards model that included propensity adjustment for surgery. Reclassification statistics including receiver operating characteristic curves and net reclassification improvement were applied to LVEF and GLS, respectively.

Results: A cohort of 190 patients met eligibility criteria. LVEF and GLS were both prognostic markers of mortality. Independent markers of 1-year mortality were *S. aureus* IE (HR:2.02; 95%CI 1.11–5.72, $p = .022$), diabetes (HR:2.05; 95%CI 1.12–3.75, $p = .020$), embolic stroke (HR:3.95; 95%CI 1.93–8.10, $p < .001$) and LVEF<45% (HR: 3.02; 95% CI 1.70–5.38, $p < .001$), GLS > −15.4% (HR:2.95; 95%CI 1.52–5.72, $p < .001$). Adding LVEF<45% to a model with known risk factors of IE did not significantly improve risk classification, whereas addition of GLS to the model resulted in significant increase (AUC = 0.763, $p < .001$).

Conclusions: When treatment was taken into account, LVEF<45% and GLS > −15.4% were both associated with adverse long-term outcome in left-sided IE. GLS > −15.4 % was significantly associated with 1-year mortality in the multivariate analysis. Further, GLS was superior to LVEF in risk prediction and risk discrimination of long-term outcome in patients with left-sided IE.

1. Introduction

Left-sided infective endocarditis (IE) is a heterogeneous disease with high complication rates and mortality [1, 2]. Both treatment and prognosis of the disease is contingent upon existing co-morbidity, presence of a cardiac device or valvular prosthesis and the virulence of the causative microorganism [3].

However, a common entity for all types of IE is the importance of cardiac deterioration at time of diagnosis. Acute heart failure of any cause is recognized as the primary reason of poor outcome in IE [3, 4]. Further, reduced systolic function measured by left ventricular ejection fraction (LVEF) has been established as a quantifiable predictor of long-term outcome in both left-sided *S. aureus* IE and streptococcal IE [5]. Accordingly, reduced cardiac function caused by heart failure in IE due to valvular dysfunction is a class 1B indication for acute surgery in IE, independent of the causative organism [3].

* Corresponding author at: Cardiovascular Research Unit II, Department of Cardiology, Herlev and Gentofte University Hospital, Kildegårdsvej 28, 2900 Hellerup, Copenhagen, Denmark.
E-mail address: trine.kiilerich.lauridsen@regionh.dk (T.K. Lauridsen).

[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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While reduced LVEF is a major complication in IE it is observed only in a subgroup of patients and even more subtle systolic impairment may be important for patient outcome. Recently, assessment of cardiac deformation using two-dimensional strain echocardiography (2DSE) has been proposed as a more sensitive marker of systolic function [8–11]. Based on this method global longitudinal strain (GLS) has proven superior in prediction of long-term outcome compared to LVEF in valvular disease and heart failure in general [12–15]. Whether measurements of cardiac deformation can predict outcome in patients diagnosed with infective endocarditis has not previously been investigated. The purposes of this study were to determine whether GLS is associated with long-term outcome and further to investigate the impact of GLS and LVEF in risk stratification of infective endocarditis.

2. Methods

2.1. Study design and patient population

The Danish Data Protection Agency and Danish Health and Medicines Authority approved the study (j.nr: 2012–58-0004 and j.nr. 3–3013-900). Current baseline and clinical data were collected from the East Danish IE Database consisting of data on prospectively collected consecutive IE patients admitted at two tertiary university hospitals in Copenhagen. Serving as referral centers for the Eastern part of Denmark, the two Danish university hospitals provide specialized care for patients with IE among ~2,400,000 total inhabitants and are highly specialized in this type of patients. The features of the East Danish Database have been described in detail previously [16].

In consideration of vendor-dependent differences in 2D strain analysis, only patients who were admitted to Gentofte University Hospital were considered for inclusion [17,18]. Patients, who were registered in the period from January 1st 2006 to December 31st 2013, were enrolled in the study. Echocardiographic quality prior to this date, in specific the acquisition frame rate of echocardiographic images (Frames/s), was considered insufficient for 2D strain analysis [19]. Only Duke definite IE patients who had high quality transthoracic echocardiograms performed were included in this study [20–21]. Patients transferred into Gentofte University Hospital and only had outside hospital echocardiograms and no GE echocardiogram available for our review were excluded from the study.

2.2. Echocardiographic data and 2D strain analyses

At admission, patients had a standard echocardiogram performed including greyscale images optimized for 2D strain analysis. All studies and offline analysis were performed with a standard imaging system and software (Vivid dimension, Vivid 7 and Vivid 9 using a 3.5 –MHz ultrasound probe EchoPac PC version BT011, (GE-Vingmed Ultrasound, Horten, Norway). 2D strain analysis was performed on gray scale images from the 4 chamber, 2 chamber and apical long-axis (APLAX) views (40–80 frames/s).

The endocardial border was traced in end-systole that placed a region of interest through the thickness of the myocardium that excluded the pericardium and tracking quality was ascertained visually as well as by the automated algorithm included in the software. In case of poor tracking, the region of interest was readjusted. Segments with persistent inadequate tracking were excluded from analysis. If >3 segments were excluded in any of the three apical views the patient was excluded from the study. The reference point was placed at the beginning of the QRS. Aortic valve closure (AVC) was defined by a pulsed wave Doppler in the LVOT using a 2 mm sample volume. Global longitudinal strain was calculated as the mean peak systolic strain in an 18-segment model from the basal, mid and apical segments, in each of the 6 walls; septal, anteroseptal, anterior, lateral, posterior, and inferior.

Further, left ventricular end-systolic volumes (LVESV), left ventricular end-diastolic volumes (LVEDV) and LVEF were assessed using the biplane Simpson's method. Finally, assessment of valvular regurgitation, valvular stenosis and chamber dimensions were performed in accordance with National guidelines and European Association of Cardiovascular Imaging guidelines [22, 23]. LVEF <45% was chosen a-priori as a cut-off based on the alterations and management strategy in heart failure with reduced systolic function [24]. Consensus on a clinical cut-off for GLS has not yet been reached. However, GLS > −16% indicates reduced contractility and studies concerning patients with HF or ischemic heart disease suggest cut-off values between −16% and −14%, thus the median GLS of −15.4% was chosen as the cut-off in this study [8–13].

2.3. Inter-observer reproducibility

Interobserver reproducibility of GLS and LVEF was assessed in a cohort of randomly selected patients. Readings for GLS was performed blinded by 2 physicians. Agreement for LVEF was performed between ECL and clinical site echocardiograms.

2.4. Statistical analyses

The association between clinical and echocardiographic variables for 1-year mortality in left-sided IE was assessed. Primary outcomes were in-hospital and 1-year all-cause mortality. Continuous variables were presented as medians with 25th and 75th percentiles. Categorical variables were presented as frequencies and percentages of the specified group. Two-sided p-values were used for all analyses and the level of statistical significance was set a priori at 0.05

2.4.1. Univariate and multivariable risk analysis

Univariate comparisons of baseline, clinical and echocardiographic characteristics according to median GLS were made with the Mann–Whitney U test or the chi-square test as appropriate. Collinearity between GLS and LVEF was analyzed with Spearman's rank correlation coefficient. Correlation exists if the coefficient is higher than 0.5. Bland Altman plots with 95% limits of agreement were generated to display inter-observer agreement for GLS and LVEF.

Kaplan–Meier survival analysis with log-rank significance test was performed to estimate overall survival differences among patients with low GLS or low LVEF, respectively. Bivariate logistic regression models were assessed to identify clinical and echocardiographic variables associated with 1-year mortality. Risk estimates for outcome are presented as hazard ratios (HRs) and 95% confidence intervals (95% CI).

2.4.2. Cox Proportional Hazard Model of 1-year mortality adjusted for treatment

To evaluate independent variables associated with long-term outcome for left-sided IE, a Cox Proportional Hazards (PH) model was fitted. The multivariate model included baseline, clinical and echocardiographic variables considered a priori to be confounders or variables of interest. A final parsimonious model was obtained by combined forward and backward selection using p < .10 for retention. This model was further weighted by inverse probability of treatment weighting (IPTW) using a propensity score for surgery calculated individually [25–26]. The propensity model included baseline variables and clinical characteristics associated with cardiac surgery; age (18–45, 46–65, >65 years), sex, causative microorganism, diabetes, kidney disease, intravenous drug use, HIV, cancer, COPD, stroke, peripheral embolization, congestive heart failure, New York Heart Association (NYHA) class, ischemic heart disease, cardiac device, bioprosthetic or mechanical heart prosthesis, any echocardiographic complication (abscess, fistula or perforation), LVEF <45%, mitral or aortic valvular regurgitation, mitral or aortic moderate/severe valvular stenosis, presence of vegetations and vegetation size. The individual patient's probability of undergoing cardiac surgery derived from this model was used as a weight in the final parsimonious Cox PH model.

To test whether information on systolic function (GLS or LVEF) would influence discrimination or reclassification of the model, receiver operating characteristic (ROC) curves, integrated diagnostic improvement (IDI), and net reclassification improvement (NRI) was performed on a model without information on systolic function (Model A), with added information on LVEF (Model B), and finally, with added information on GLS (Model C) [27, 28].

All statistical analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC) or R for Mac OS X (Version 0.97.551, http://www.R-project.org/).

3. Results

3.1. Baseline clinical and echocardiographic features

Of 304 IE cases admitted to Gentofte University Hospital in the period 2006–2013, 190 patients met eligibility criteria for the current study (Fig. 1). Baseline and clinical characteristics of the study population stratified by median GLS are shown in Table 1. Patients with impaired GLS (> − 15.4%) were more likely to have a history of congestive heart failure (28.0% vs. 4.1%, p < .001), ischemic heart disease (35.5% vs. 11.3%, p < .001), and prosthetic heart valve (39.8% vs. 7.2%, p < .001). Patients with GLS > −15.4% were less likely to undergo cardiac surgery during admission (31.2% vs. 54.6%, p = .002). Echocardiographic characteristics stratified by median GLS are displayed in Table 1.

Patients with impaired GLS had significantly higher left ventricular end-systolic volume (LVESV) than patients with normal GLS (81.5 ml vs. 61.5 ml, p < .001), were less likely to have a vegetation present (91.8% vs. 80.6%, p < .001), or to be diagnosed with severe mitral regurgitation at admission (9.9% vs. 22.9%, p = .036).

To examine whether collinearity existed between LVEF and GLS, a scatterplot with outcome variables and Spearman correlation analysis was performed. LVEF and GLS were highly correlated, spearman rank correlation coefficient = −0.719, p < .001, which should be noted in a multivariate model.

3.2. Inter-observer agreement

Interobserver agreement was assessed in a random sampled cohort of 20 subjects. The reproducibility of GLS was excellent which is