Role of Global Longitudinal Strain in the Prediction of Outcome in Patients With Severe Aortic Valve Stenosis

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In the present study, we assessed the role of Global Longitudinal Strain (GLS) as a predictor of all-cause mortality in patients with severe aortic valve stenosis (AS), irrespective of their type of treatment. Data of 807 patients with AS receiving complete echocardiographic and clinical examination were retrospectively analyzed. Valve area <1 cm^2 and sufficient image quality were inclusion criteria; patients with severe concomitant valvulopathy were excluded. Patients were grouped into treatment (aortic valve replacement [AVR]) and conservative (non-AVR) groups. Multivariable Cox analysis was used to assess predictors of all-cause mortality. Five hundred fourteen patients were included and 53.3% were of male gender. Mean age at inclusion was 76.4 ± 9.8 years; 326 received AVR. Death from any cause occurred in 72.9% of non-AVR group and 17.8% of AVR group (p <0.001). GLS (expressed as |%|) was found to be an independent predictor of all-cause mortality in non-AVR group (hazard ratio [HR] 0.933, 95% CI 0.854 to 0.987, p = 0.038). In patients receiving AVR, GLS and history of coronary artery bypass graft were found to be independent predictors of all-cause mortality (HR for GLS 0.912, 95% CI 0.730 to 0.999, p = 0.048; HR for coronary artery bypass graft 2.977, 95% CI 1.014 to 6.273, p = 0.013). In non-AVR patients, GLS <9.7% showed a higher 1- and 5-year mortality (log rank p values of 0.002 and 0.010, respectively). In conclusion, GLS is an independent predictor of all-cause mortality in severe AS, irrespective of their type of treatment. GLS <9.7% indicates a significantly higher 1- and 5-year mortality in non-AVR patients. Therefore, GLS should be regularly assessed for enhanced risk stratification and clinical decision-making. **(Am J Cardiol 2017;120:640−647)**

Conventional parameters of left ventricular (LV) function such as LV ejection fraction (LVEF) and mitral annular plane systolic excursion (MAPSE) have been established for many years and proved their reliability. Global longitudinal strain (GLS) has yet to proof its value and relevance for clinical decision-making. GLS can be measured in 2 dimensional (2D) echocardiography using speckle tracking and is defined as the relative change in myocardial length over 1 heart cycle from end-diastole to end-systole. The American Society of Echocardiography and the European Association for Cardiovascular Imaging endorse all 3 parameters in the latest recommendations for chamber quantification.[1] For LVEF exist the most reference values, but measurements are highly preload and afterload dependent. Since the first reports on measurements of MAPSE in the late 1960s by Zaky et al,[2] the M-mode measurement has evolved into a recognized surrogate parameter for systolic LV function, being a recommended alterative especially in patients with poor image quality.[1] Less experience exists with GLS and normal values are vendor specific. Before using new measurements in every day clinical routine, a parameter should be carefully evaluated in large cohorts with different vendor software tools. A correlation of GLS with all-cause mortality has been shown in different disease entities. Recent publications suggest this finding to be reproducible in the case of aortic valve stenosis (AS), but these findings were limited to subgroups of AS with specific LVEF or transvalvular gradients.[3−5] Therefore, the aim of this study was to show that GLS is a robust LV functional parameter for patients' outcome in the day-to-day clinical practice in full range of transvalvular pressure gradients and independently of LVEF. This assumption was tested in both conservatively treated patients and in patients receiving aortic valve replacement (AVR).

Methods

All patients with severe native AS and sufficient image quality for 2D speckle-tracking analysis presenting at our tertiary center university hospital between 2005 and 2012 who gave written consent were retrospectively included (n = 807). One hundred fifteen patients were excluded due to insufficient image quality. We furthermore excluded 103 patients with a native aortic valve area of ≥ 1.0 cm^2 and 46 patients with concomitant valvulopathies grade III. Twenty-nine patients were lost to follow-up, resulting in a final study population of n = 514 patients.

AVR applies to both surgical and transcatheter valve replacement. Hypertension was presumed to be present when antihypertensive medication was prescribed or office

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blood pressure was recorded above 140/90 mm Hg. Significant coronary artery disease was presumed to be present when >50% stenosis in at least 1 coronary artery bed was recorded or a history of myocardial infarction, percutaneous intervention, or coronary artery bypass graft (CABG) was documented. Obesity was defined as body mass index $\geq$ 30 kg/m^2 and hypercholesterolemia as total cholesterol > 200 mg/dl. New York Heart Association functional classification was used to classify the clinical symptom status. Approval of local ethics committee was obtained.

The clinical data were obtained from physician reports in our hospital database recorded at the time of presentation. Survival status was assessed through telephone interviews with the patient or a family member, conducted from February 2013 to June 2013 or by inspection of death certificates. For outcome assessment in patients treated conservatively, we used the time from baseline echocardiography to end of study (telephone interview) or death. For patients receiving AVR meanwhile, we used the date of AVR as a baseline to avoid a selection bias. The end of study was the same for both groups.

All patients received a complete transthoracic echocardiographic examination in supine left lateral position using a 3.5-MHz transducer. The data were stored on dedicated workstations for offline analysis (Vivid 7 and E9 System; GE Vingmed Ultrasound, Horten, Norway). Chamber quantification was performed as follows, applying the respective guideline.[1] In parasternal long-axis view, the diameter of the LV outflow was measured as distance between the aortic valve hinge points in mid-systole using B-mode. Ventricular and septal diameter as well as posterior wall thickness was measured at end-diastole at the height of the papillary muscles tips. LV mass was calculated by integrating LV dimensions in the appropriate formula proposed by the American Society of Echocardiography and indexed for body surface area. Relative wall thickness was defined as the ratio of 2 times the diastolic thickness of the posterior LV wall and the internal LV diameter.

In apical 4-chamber view, early (E) and atrial (A) wave patterns were documented by measuring diastolic mitral valve inflow at the height of the mitral valve tips. The tissue Doppler−derived value for the early diastolic velocity of septal and lateral portion of the mitral annulus in apical 4-chamber view was averaged and denoted E′. E/E′ was used as estimate for LV end-diastolic filling pressures. Using M-mode, MAPSE and tricuspid annular plane systolic excursion were measured. MAPSE was measured in both the septal and lateral mitral annulus and averaged. LVEF was calculated from apical 2- and 4-chamber views using Simpson's biplane method. Severity of AS was defined as aortic valve area <1 cm^2 using the continuity equation.

Stroke volume was measured in the LV outflow tract using pulsed wave Doppler velocity profiles coinciding with measurement of brachial blood pressure measurement by arm-cuff sphygmomanometer. Cardiac index was calculated as stroke volume multiplied with heart rate, divided by body surface area. The ratio of stroke volume indexed to the body surface area and pulse pressure yields systemic arterial compliance. The sum of systolic artery pressure and the mean transvalvular pressure gradient divided by stroke volume indexed to the body surface area yields the valvuloarterial impedance. For calculation of body surface area, Mosteller's formula was used.

Using 2D speckle-tracking analysis, measurement of GLS was performed offline by experienced cardiologists (B.F. and S.H.) using raw data files (EchoPAC, version 113; GE Healthcare, Horton, Norway). The endocardial border was traced manually in apical 4-, 3-, and 2- chamber views, adjusting the width of the region of interest to the myocardial wall thickness obtaining measurements of 6 myocardial segments in each view. Only segments of sufficient image quality (i.e., >55 frames per second) were used for the final analysis. GLS was defined as the average of the obtained strain values in the respective myocardial segments and will be expressed in absolute values (|%|) with higher values indicating higher myocardial deformation (Figure 1).[5]

For the comparison of categorical data, the chi-square test and Fisher's exact test were used as appropriate. We used 1-way analysis of variance to analyze differences in continuous data, if normal distribution was ascertained by Kolmogorov-Smirnov test. If the assumption of normal distribution was violated, the Kruskal-Wallis test was used.

Univariable Cox regression analysis was used to calculate the hazard ratio (HR) for all-cause mortality for clinical and echocardiographic parameters, using the time from baseline echocardiography to death or follow-up in the non-AVR group. In the AVR group, only the time after valve replacement was used for outcome analysis. Analysis was conduced for groups of parameters representing similar aspects of echocardiographic and clinical measurements. For multivariable Cox regression, we used all parameters that have been shown to be of significant influence on outcome in the univariable regression analysis. If a significant correlation within 1 group was noted (Pearson/Spearman's test), only the parameter with the highest influence on the outcome was incorporated in further analysis. In the first step of multivariable regression analysis for all-cause mortality, the parameters were entered in groups after adjustment for age and gender, using a forward stepwise (likelihood ratio) method. All parameters significantly associated with the outcome were pooled together for a second step, using the same method as in step 1. Patients with previous malignancy were excluded from multivariable analysis because of its uneven distribution between the 2 groups and its influence on all-cause mortality. If no adjustment for history of malignancy was performed, it remained as single independent predictor of mortality in the group of patients receiving valve replacement.

For mortality analysis, we defined the GLS to be significantly reduced when below the 25th percentile of the whole cohort, that is, GLS <9.7 |%|. Differences in mortality were tested with log-rank test (Mantel Cox) and displayed as Kaplan-Meier plots. For mortality analysis, we used the time from baseline to death from any cause or end of study (telephone interview) in the non-AVR group, for the patients receiving AVR, we used the time from AVR to death from any cause or end of study (telephone interview).

A p value of <0.05 was considered statistically significant. All statistical analysis was conducted with SPSS, version 22 and 23 (SPSS Inc., Chicago, Illinois).