Relationship between Longitudinal Strain and Symptomatic Status in Aortic Stenosis

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Background: Global longitudinal strain (GLS) and basal longitudinal strain (BLS) assessed using two-dimensional speckle-tracking imaging have been proposed as subtle markers of left ventricular (LV) systolic dysfunction with potential prognostic value in patients with aortic stenosis (AS). The aim of this study was to evaluate the relationship between longitudinal strain and symptomatic status in patients with AS.

Methods: GLS and BLS were measured in 171 patients with pure, isolated, at least mild AS prospectively enrolled at two institutions. The population was divided into four groups: asymptomatic nonsevere AS ($n = 55$), asymptomatic severe AS with preserved LV ejection fraction (LVEF; $\geq$50%) ($n = 37$), symptomatic severe AS with preserved LVEF ($n = 60$), and severe AS with reduced LVEF (<50%) ($n = 19$).

Results: GLS was significantly different among the four groups ($P < .0001$), but the difference was due mainly to patients with reduced LVEFs. In addition, there was an important overlap among the groups, and in multivariate analysis, after adjustment for age, gender, AS severity, and LVEF, GLS was not an independent predictor of symptomatic status ($P = .07$). BLS was also significantly different among the four groups ($P < .0001$) but in contrast was independently associated with symptomatic status ($P < .0001$). However, as for GLS, there was an important overlap between groups and differences were close to intraobserver or interobserver variability (1.3 $\pm$ 1.1% and 2.0 $\pm$ 1.6%, respectively).

Conclusions: In this prospective multicenter cohort of patients with wide ranges of AS severity, symptoms, and LVEFs, BLS but not GLS was independently associated with symptomatic status. However, there was an important overlap among groups, and differences were close to measurements' reproducibility, raising caution regarding the use of longitudinal strain, at least as a single criterion, in the decision-making process for patients with severe asymptomatic AS. (J Am Soc Echocardiogr 2013;26:868-74.)

Keywords: Aortic stenosis, Echocardiography, Longitudinal strain, Speckle-tracking

Current guidelines recommend surgery in patients with severe aortic stenosis (AS) and symptoms, abnormal exercise test results, and/or reduced left ventricular (LV) systolic function as defined by a LV ejection fraction (LVEF) < 50%.[1,2] In contrast, management of asymptomatic patients with severe AS remains debated, and recent research has focused on the identification of subsets of patients who may benefit from "prophylactic" or early surgery.

Patients with overt LV systolic dysfunction who undergo surgery incur excess morbidity and mortality,[3] but LVEF can be preserved despite reduced myocardial contractility.[4] Two-dimensional strain and strain rate imaging have been proposed as more sensitive modalities to ascertain LV myocardial contractility.[5] Previous studies have suggested that global longitudinal strain (GLS) and basal longitudinal strain (BLS) assessed using two-dimensional speckle-tracking imaging are associated with AS severity and are independent predictors of outcomes.[6-8] Mechanisms of symptom occurrence in patients with severe AS are complex and may involve both systolic and diastolic LV dysfunction, but one may expect, if longitudinal strain is independently linked to outcome, that it should accurately differentiate symptomatic patients with severe AS from those who are asymptomatic or have nonsevere AS. However, studies examining the relationships among longitudinal strain, AS severity, ejection fraction, and symptoms are impeded by relatively small sample sizes and, more important, by the enrollment of selected patients and the exclusion of

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Abbreviations

ALS = Apical longitudinal strain

AS = Aortic stenosis

AUC = Area under the receiver operating characteristic curve

AVA = Aortic valve area

BLS = Basal longitudinal strain

CAD = Coronary artery disease

COFRASA = Aortic Stenosis in Elderly: Determinant of Progression

GENERAC = Genetic of Aortic Valve Stenosis: Clinical and Therapeutic Implications

GLS = Global longitudinal strain

LV = Left ventricular

LVEF = Left ventricular ejection fraction

MPG = Mean pressure gradient

symptomatic patients or those with reduced LVEFs. Thus, the aim of the present study was to assess the relationship between longitudinal strain and symp-toms in a large cohort of patients with wide ranges of AS severity and LVEF.

METHODS

Study Population

We prospectively enrolled patients with AS at two institutions (Bichat Hospital, Paris, France, and Henri-Mondor Hospital, Creteil, France) from February 2009 to June 2010. The inclusion criterion was pure, at least mild AS (defined by a mean pressure gradient [MPG] > 10 mm Hg). Exclusion criteria were more than mild coexisting aortic regurgitation (defined by a vena contracta width ≥ 3 mm or a regurgitant volume ≥ 30 mL)[9] or other valvular heart disease, segmental LV wall motion abnormality and/or prior myocardial infarction, atrial fibrillation, and poor ultrasound window.

Clinical evaluation included demographic data, cardiovascular risk factors, physical examination, and assessment of AS-related symptoms (dyspnea, angina, and syncope). Blood pressure was measured using an arm-cuff sphygmomanometer at the time of the Doppler echocardiographic examination. History of coronary artery disease (CAD) was defined as previous myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft surgery. Coronary angiography was performed mainly as a preoperative test before conventional surgery or transcatheter aortic valve implantation. Significant CAD was defined as a >50% reduction in luminal diameter in the left main coronary artery and a >70% reduction in the other branches.

Informed consent was obtained from all patients, and the study was approved by both institutional review boards. Bichat Hospital's patients were enrolled in two ongoing prospective studies (Aortic Stenosis in Elderly: Determinant of Progression [COFRASA], ClinicalTrials.gov identifier NCT00338676, and Genetic of Aortic Valve Stenosis: Clinical and Therapeutic Implications [GENERAC], ClinicalTrials.gov identifier NCT00647088).

Conventional Doppler Echocardiography

Comprehensive transthoracic echocardiography was performed in all patients by experienced operators using a Vivid 7 system (GE Vingmed Ultrasound AS, Horten, Norway).

AS Severity. Evaluation of AS severity was performed on the basis of peak velocity, MPG, and aortic valve area (AVA) calculated using the continuity equation.[10] Severe AS was defined as AVA < 1 cm^2.

LV Size and Function. LV diameters were measured in the parasternal long-axis view using M-mode imaging. LV mass was calculated using Devereux's formula and indexed to body surface area. LV hypertrophy was defined as an LV mass index > 95 g/m^2 in women and > 115 g/m^2 in men.[11] LVEF was assessed using the biplane Simpson's method or visually. LV systolic dysfunction was defined as an LVEF < 50%. Systolic pulmonary artery pressure was calculated using continuous-wave Doppler, and right atrial pressure was estimated on the basis of inferior vena cava size and changes during inspiration.

Systemic Arterial Hemodynamics. LV stroke volume was calculated as the product of LV outflow tract area and LV outflow tract time-velocity integral. LV stroke volume index was obtained by dividing stroke volume by body surface area. Cardiac output was calculated by multiplying stroke volume by heart rate and cardiac index as cardiac output divided by body surface area. Systemic arterial compliance was calculated as LV stroke volume index / (systolic − diastolic blood pressure).[12] Systemic vascular resistance was calculated as (80 × mean blood pressure)/cardiac output. Valvuloarterial impedance was calculated as suggested by Hachicha *et al.*[13] as (MPG + systolic blood pressure)/LV stroke volume index.

Two-Dimensional Speckle-Tracking Imaging

Apical two-chamber, three-chamber, and four-chamber views were acquired and digitally stored on a dedicated workstation for offline analysis. All images were obtained at a frame rate ≥ 50 frames/sec. Longitudinal strain was measured using EchoPAC software (GE Vingmed Ultrasound AS) in the three apical views over three cardiac cycles and averaged. The operator manually identified three points in each of the three apical views, one at the apex and two on each side of the mitral valve. The software then automatically tracked the endocardial borders. The region of interest or the endocardial borders were manually adjusted to optimize tracking if needed. Inadequately tracked segments were excluded from analysis. The left ventricle was divided into 18 segments, six basal, six medial, and six apical segments. Each segment was individually analyzed. Apical longitudinal strain (ALS), medial longitudinal strain, and BLS were calculated as the means of peak systolic longitudinal strain of the six apical, medial, and basal segments, respectively, and GLS was calculated as the mean of the peak systolic longitudinal strain of all 18 segments. Because BLS may be a more sensitive marker of LV systolic dysfunction, the BLS/ALS ratio was also analyzed. Measurements were performed by two operators (D.A., L.M.) blinded to any clinical and transthoracic echocardiographic data.

Statistical Analysis

Data are presented as mean ± SD or as numbers and percentages. We divided our population into four groups according to AS severity, symptoms, and LVEF: asymptomatic patients with nonsevere AS, asymptomatic patients with severe AS and preserved LVEFs, symptomatic patients with severe AS and preserved LVEFs, and patients with severe AS and reduced LVEFs (<50%). Comparisons between groups were performed using one-way analysis of variance or χ^2 tests as appropriate. Comparisons between strain measurements and AS severity or LVEF were performed using linear regressions. Area under the receiver operating characteristic curve (AUC) for the diagnosis of severe symptomatic AS was calculated for global and segmental longitudinal strain. The association between longitudinal strain and symptomatic status was assessed using logistic regression after adjustment for age, gender, AS severity, and ejection fraction. Analyses were performed in the overall population and in subgroups according to LVEF or history of CAD. Intraobserver and