Structural Heart
The Journal of the Heart Team

ISSN: 2474-8706 (Print) 2474-8714 (Online) Journal homepage: https://www.tandfonline.com/loi/ushj20

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To cite this article: Maria Melissopoulou, Virginia Nguyen, Julien Dreyfus, David Attias, Sarah Tubiana, Xavier Duval, Isabelle Codogno, Claire Cimadevilla, Alec Vahanian & David Messika-Zeitoun (2017) Determinants and Prognostic Value of Longitudinal Strain in Asymptomatic Aortic Stenosis and Preserved Left Ventricular Ejection Fraction—The COFRASA/GENERAC Study, Structural Heart, 1:3-4, 182-187, DOI: 10.1080/24748706.2017.1356491

To link to this article: https://doi.org/10.1080/24748706.2017.1356491

Accepted author version posted online: 24 Jul 2017.
Published online: 27 Jul 2017.

STRUCTURAL HEART
2017, VOL. 1, NOS. 3–4, 182–187
https://doi.org/10.1080/24748706.2017.1356491

ORIGINAL RESEARCH

Determinants and Prognostic Value of Longitudinal Strain in Asymptomatic Aortic Stenosis and Preserved Left Ventricular Ejection Fraction—The COFRASA/GENERAC Study

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ABSTRACT

Background: Longitudinal strain has been proposed as a sensitive marker of left ventricular systolic dysfunction. However its prognostic value in patients with aortic stenosis (AS) remains debated.

Methods: In a prospective cohort of asymptomatic patients with at least mild, isolated AS and preserved left ventricular ejection fraction (LVEF), clinical, biological measurements, global longitudinal strain (GLS) and basal longitudinal strain (BLS) were performed at study entry. The occurrence of AS-related events (sudden death, congestive heart failure, new onset of symptoms) or aortic valve replacement within two years was recorded prospectively.

Results: A total of 140 patients were enrolled and 21 events occurred. In contrast to GLS, BLS was significantly correlated to AS severity ($p = 0.0006$ with PV, $p = 0.0002$ with MPG, $p = 0.01$ with AVA, and $p = 0.0009$ with AVAi) and predicted the occurrence of AS-related events in the subset of severe AS in univariate analysis ($p = 0.03$) and after adjustment for AVA ($p = 0.01$), AVAi ($p = 0.01$), PV ($p = 0.045$), and MPG ($p = 0.05$). However, there was an important overlap of baseline BLS values between patients who developed symptoms and those who did not and repeated BLS measurements showed no difference between baseline values and those obtained at the time of overt symptoms in nine patients ($p = 0.38$).

Conclusion: BLS was statistically predictive of AS-related events in the subset of severe AS. However, overlap of BLS values between groups of symptomatic status and similar values at baseline and at the time of overt symptoms raise the question of its use at an individual level at least as a single isolated parameter.

ARTICLE HISTORY Received 13 March 2017; Accepted 13 July 2017

KEYWORDS Aortic stenosis; echocardiography; longitudinal strain; prognosis

Introduction

Aortic stenosis (AS) is the most frequent type of valvular heart disease in Europe and North America. Current recommendations for aortic valve replacement (AVR) in severe AS are based on the presence of symptoms or left ventricular (LV) systolic dysfunction defined as LV ejection fraction (LVEF) <50%.[1,2] However, the onset of symptoms is often insidious and treatment of asymptomatic patients remains controversial. Thus, objective markers allowing improving risk stratification of asymptomatic AS patients to identify high-risk patients that may benefit from an early—or prophylactic—surgery are highly desirable.

LVEF is a late and insensitive marker of global LV systolic dysfunction. It has been suggested that longitudinal strain (LS) assessed by speckle tracking echocardiography may be a more sensitive marker of LV systolic dysfunction than LVEF and was associated with AS severity.[3] Prognostic value of global longitudinal strain (GLS) is inconstant in the literature[4–6] whereas basal longitudinal strain seems to be a more powerful predictor of outcomes in AS patients.[7–9] Prospective studies with asymptomatic AS are needed to determine whether low values of LS translate into poor predictive value. Thus, the aim of this prospective study was to investigate the prognostic value of global and regional LS in asymptomatic AS patients with preserved LVEF and to assess its potential clinical usefulness in patients' management.

Materials and methods

Study design

Our study population consisted of asymptomatic patients with pure, isolated, at least mild (MPG ≥10 mmHg) degenerative AS who underwent an echocardiography examination using a GE imaging system and who were prospectively enrolled in an ongoing cohort, COFRASA/GENERAC

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(clinicalTrial.gov number NCT 00338676 and clinicalTrial.gov number NCT00647088), which is designed to evaluate the determinants of AS occurrence and progression. Exclusion criteria were rheumatic or radiotherapy-related AS, history of infective endocarditis, more than mild associated aortic regurgitation or other valvular disease, and severe respiratory disease or renal failure (creatinine clearance ≤ 30 ml/min). Patients with symptoms (dyspnea, angina or syncope/presyncope) even atypical were excluded. Transthoracic echocardiography and clinical evaluation were performed at baseline. Patients were contacted every 6 months and seen yearly at our research center. Further exclusion criteria, related to the present longitudinal strain study using 2D speckle tracking imaging, were atrial fibrillation, complete left brunch block, pacemaker, depressed LVEF defined as an LVEF<50%, segmental LV wall motion abnormalities and inadequate imaging for strain measurement. Occurrence of AS-related events—sudden death, congestive heart failure, new onset of symptoms (dyspnea, angina or syncope)—or performance of an aortic valve replacement was prospectively recorded. Assessment of symptoms was performed by experienced cardiologists blinded of echocardiographic strain measurements. Strain measurements were repeated 1 or 2 years apart in patients who became symptomatic and were seen at our research center. The regional ethic committees approved the protocol, and all patients gave written informed consent.

Clinical assessment

Medical history, cardiovascular risk factors and medication were prospectively recorded. A physical examination including blood pressure measurement and electrocardiogram was performed at study entry. Patients had to be free of dyspnea, angina, and syncope.

Echocardiographic measurements

Conventional parameters

A comprehensive two-dimensional and Doppler echocardiography was performed using a Vivid 7 imaging system (GE Healthcare). AS severity was evaluated based on peak aortic velocity (PV), mean pressure gradient (MPG) and the aortic valve area (AVA) using the continuity equation as recommended by current guidelines.[10] The AVA was calculated as an absolute value and indexed (AVAi) to body surface area. Severe AS was defined by MPG > 40 mmHg. LV mass was calculated using Devereux's formula.[11] Cine loops of apical 4-, 3- and 2-chamber, parasternal long-axis, and short-axis views were obtained and the LVEF was determined visually or using the Simpson method. Mitral inflow velocities (E- and A-waves) using pulsed-wave Doppler and mitral annular velocities (E'-wave) using pulsed-wave tissue Doppler imaging at the septal level were recorded in the apical four-chamber view. Diastolic function was assessed based on E/A and E/E' ratios. The left atrial volume was calculated using the biplane area length formula as recommended.[12]

Two-dimensional speckle-tracking imaging

Apical two-, three-, 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. LS was measured using EchoPAC software (GE Vingmed Ultrasound AS) in the three apical views. The operator manually identified three endocardial points in each of the three apical views, one at the apex and two on each side of the mitral annulus. The software then automatically tracked the endocardial borders. The region of interest of the endocardial borders was manually adjusted to optimize tracking if needed. The left ventricle was divided into 18 segments, six basal, six medial, and six apical segments. Each segment was individually analyzed. Inadequately tracked segments were excluded from analysis (no more than one per view). The global longitudinal strain (GLS) was calculated as the mean of the peak end-systolic (defined at the aortic valve closure) longitudinal strain of all 18 segments and basal longitudinal strain (BLS) as the mean of the six basal segments.[13] Measurements were performed by three operators (J.D., V.N., M.M.) blinded of any baseline and follow-up clinical, biological, and transthoracic echocardiographic data.

Laboratory analysis

All blood samples were taken at inclusion under identical conditions, at 08.00 am, after a 12-hour-fast, the same day of the echocardiography and were immediately processed. N-terminal fragment of pro B-type natriuretic peptide (Nt-proBNP) was measured by chemiluminescent immunoassay (Dimension Vista, Siemens). Glomerular filtration rate was calculated using the modified diet in renal disease (MDRD) formula.

Statistical analysis

Normality distribution was tested using the Kruskal-Wallis test. Continuous variables were expressed as the mean ± standard deviation or as the median (interquartile range) and qualitative data as number of patients (percentages). Comparisons between groups were performed using t-test, one-way analysis of variance, Chi-square or Wilcoxon/Kruskal-Wallis tests as appropriate. Correlations between strain measurements and clinical, echocardiographic, biological data were performed using linear regression. Univariate and stepwise multiple linear regression analysis were used to identify determinants of both GLS and BLS. Only variables with a p value <0.20 in univariate analysis were entered in the model. Event-free survival for composite endpoint of AS-related events (defined by sudden death, congestive heart failure, new onset of symptoms) or for AVR was assessed using the Kaplan-Meier analysis. Comparisons of event-free survival according to medial GLS or BLS values were performed by means of log-rank test. Cox proportional-hazard analyses evaluated the predictive value of GLS and BLS for event-free survival in univariate analysis and after adjustment for AS severity. Repeated measures of GLS and BLS were compared using paired t-test. Intra-observer and inter-observer variability of GLS and BLS measurements was calculated as the mean absolute difference between measurements in 20 randomly selected patients. All

tests were two-sided and performed using JMP7® software. A p value < 0.05 was considered statistically significant.

Results

Population characteristics

A total of 140 patients were enrolled prospectively. Baseline characteristics of the population are presented in Table 1. Ninety-seven were male (69%) and the mean age was 73 ± 10 years. Mean MGP was 30 ± 18 mm Hg (median 25 mm Hg, [17–41]), mean peak aortic valve velocity was 342 ± 86 cm/s (median 320, [279–396]), mean AVA 1.22 ± 0.34 cm^2 (median 1.20, [0.96–1.49]) and mean AVAi 0.66 ± 0.17 cm^2/m^6 (median 0.66, [0.53–0.79]). Overall, 66 patients (47%) had mild AS, 39 patients (28%) moderate AS and 35 patients (25%) severe AS.

Table 1. Clinical, echocardiographic and biological characteristics of the population overall and by events.

	Overall (N = 140)	Events (+) (n = 21)	Events (–) (n = 119)	p value[a]
Age (years)	73 ± 10	72 ± 10	73 ± 10	0.75
Men	97 (69)	16 (76)	81 (68)	0.47
Body mass index, kg/m^2	27 ± 4	27 ± 4	27 ± 5	0.91
Heart rate, beats/min	66 ± 11	67 ± 10	66 ± 11	0.50
Hypertension	91 (65)	16 (76)	75 (63)	0.22
Diabetes mellitus	26 (19)	4 (19)	22 (18)	0.99
Hypercholesterolemia	83 (59)	15 (71)	68 (57)	0.18
Aortic stenosis grade				
Mild	66 (47)	1 (5)	65 (55)	
Moderate	39 (28)	4 (19)	35 (29)	<0.0001
Severe	35 (25)	16 (76)	19 (16)	
Pic aortic velocity, m/sec	3.4 ± 0.9	4.4 ± 0.9	3.2 ± 0.7	<0.0001
Mean pressure gradient, mm Hg	30 ± 18	51 ± 21	26 ± 14	<0.0001
Aortic valve area, cm^2	1.22 ± 0.34	0.97 ± 0.26	1.27 ± 0.33	<0.0001
Indexed aortic valve area, cm^2/m^2	0.66 ± 0.17	0.51 ± 0.12	0.69 ± 0.17	<0.0001
E/A	1.00 ± 0.93	0.9 ± 0.4	1.0 ± 0.9	0.17
E/E'	13.5 ± 4.6	14.4 ± 5.6	13.4 ± 4.5	0.68
Left atrial indexed volume, mL/m^2	48 ± 13	52 ± 9	47 ± 13	0.07
Systolic pulmonary artery pressure, mm Hg	30 ± 5	31 ± 5	30 ± 6	0.29
Left ventricular mass index, g/m^2	121 ± 34	135 ± 32	118 ± 33	0.02
|GLS|, %	21.9 ± 2.5	21.2 ± 2.0	22.0 ± 2.6	0.14
|BLS|, %	17.0 ± 3.4	15.1 ± 3.3	17.3 ± 3.4	0.007
Nt-proBNP, pg/mL	351 ± 838	450 ± 444	318 ± 835	0.004
Serum creatinine, µmol/L	90 ± 26	93 ± 25	89 ± 27	0.45

Note. Data are expressed as mean ± standard deviation (SD), or number (percentage).
[a]p value for patients who presented an AS-related event versus patients without an AS-related event.

Determinants of longitudinal strain

Global longitudinal strain

Mean value of GLS was −21.9 ± 2.5% (−21.9 [−23.6 to −20.3]). When considering each covariate independently, GLS was significantly associated to body mass index (BMI) (p = 0.006) but not to age (p = 0.18), sex (p = 0.93), AS severity (p = 0.77 with PV, p = 0.99 with MPG, p = 0.42 with AVA and p = 0.81 with AVAi) (Figure 1A), heart rate (p = 0.13), E/A ratio (p = 0.67), E/E' ratio (p = 0.055), systolic pulmonary artery pressure (p = 0.13), indexed LV mass (p = 0.51), indexed left atrial volume (p = 0.85) and Nt-proBNP values (p = 0.52). When a logistic regression model was performed, the only independent determinant of GLS was BMI (p = 0.004).

Basal longitudinal strain

Mean value of BLS was −17.0 ± 3.4 % (−17.2 [−19.0 to −15.0]). When considering each covariate, BLS was associated to AS severity (p = 0.0006 with PV, p = 0.0002 with MPG, p = 0.01 with AVA and p = 0.0009 with AVAi) (Figure 1B), heart rate (p = 0.0001), E/A ratio (p = 0.04) and E/E' ratio (p = 0.004). BLS was not associated with BMI (p = 0.19), systolic pulmonary artery pressure (p = 0.45), age (p = 0.58), sex (p = 0.54), indexed LV mass (p = 0.15), indexed left atrial volume (p = 0.44) and Nt-proBNP values (p = 0.58). Independent determinants of BLS were AS severity (p = 0.04 with PV, p = 0.02 with MPG, p = 0.15 with AVA and p = 0.01 with AVAi), heart rate (p = 0.008), E/A ratio (p = 0.03) and E/E' ratio (p = 0.03).

Prognostic value of longitudinal strain

Among the 140 patients enrolled, 21 patients had an AS-related event within the 2 years of follow-up, four patients developed angina and 17 patients developed dyspnea. No sudden death occurred during follow-up. Among the 21 patients who had an AS-related event, 16 occurred in the subset of patients with severe AS, four occurred in this subset of patients with moderate AS and only one occurred in the subset of patients with mild AS. Eighteen of the symptomatic patients underwent an AVR while three patients remained under conservative management due to

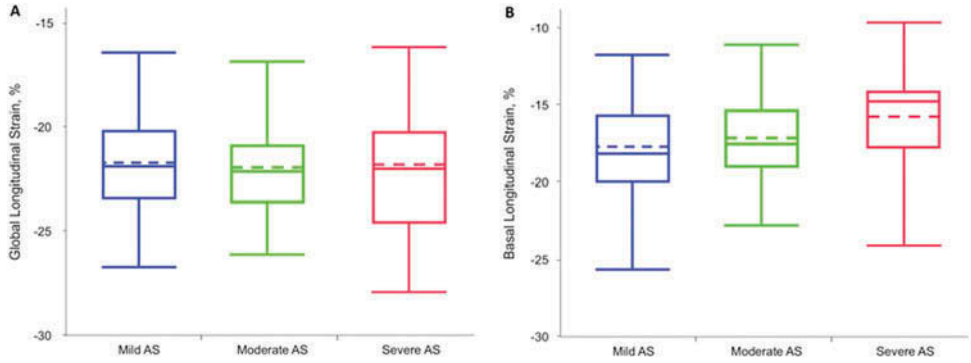

Figure 1. Comparisons of (A) global longitudinal strain values and (B) basal longitudinal strain values according to groups of severity of aortic stenosis. The box defines the interquartile range with the median indicated by the full line and the mean indicated by the dotted line.

comorbidities or patient preferences. Two other patients underwent a prophylactic AVR. Symptoms-free survival was 92% at one year and 84% at 2 years. AVR-free survival was 91% at one year and 85% at 2 years.

Global longitudinal strain

GLS values were similar between patients who developed symptoms and those who remained asymptomatic (−21.2 ± 2% vs. −22 ± 2.6%, $p = 0.14$) (Figure 2A). Symptoms-free survival curves at 2 years were similar according to the median value of GLS (83% with GLS < |21.9% and 85% with GLS > |21.9%, $p = 0.89$) (Figure 3A). In univariate analysis, GLS was not associated with symptoms-free survival ($p = 0.20$). In multivariate analysis, AS severity was predictive of symptoms-free survival (all $p < 0.0001$) but not GLS (all $p > 0.05$). Similar results were obtained when occurrence of AVR was considered as end-point ($p = 0.22$) and when the analysis was restricted to the subset of 35 patients with severe AS (16 events, $p = 0.16$).

Basal longitudinal strain

BLS was significantly lower in patients who presented an AS-related event during follow-up (−15.1 ± 3.2% vs. −17.3 ± 3.4%, $p = 0.008$) (Figure 2B). However, BLS values were widely scattered with a large overlap between the two groups. Symptoms-free survival curves at 2 years were different according to the median value of BLS (74% with BLS < |17% and 92% with BLS > |17%, $p = 0.001$) (Figure 3B). In univariate analysis BLS was predictive of symptoms-free survival (HR, 1.18 [1.05–1.32], $p = 0.007$). In multivariate analysis, BLS was an independent predictor of symptoms-free survival after adjustment for AVA ($p = 0.049$) but not after adjustment for PV ($p = 0.50$), MPG ($p = 0.46$) or AVAi ($p = 0.08$). BLS tended to be associated with symptoms-free survival or occurrence of AVR but did not reach statistical significance ($p = 0.07$). In the subset of severe AS, BLS was predictive of symptoms-free survival in univariate analysis (HR, 1.16 [1.02–1.32], $p = 0.03$) and after adjustment for AVA (HR, 1.2 [1.04–1.41], $p = 0.01$), AVAi (HR, 1.19 [1.03–1.38], $p = 0.01$), PV (HR, 1.2 [1.00–1.48], $p = 0.045$) and MPG (HR, 1.18 [1.00–1.44], $p = 0.05$).

Repeated measurements

GLS and BLS were re-measured while patients presented with overt symptoms in nine patients and both GLS and BLS values were not significantly different from baseline values (−23.0 ± 3.0% vs. −21.7 ± 1.7%, $p = 0.16$ and −17.0 ± 1.3% vs. −17.8 ± 2.8%, $p = 0.38$ respectively).

Reproducibility of longitudinal strain measurements

Intraobserver and interobserver variability of strain measurements (absolute difference) was 0.60 ± 0.40% and 0.98 ± 0.69% for GLS and 0.60 ± 0.38% and 0.96 ± 0.69% for BLS.

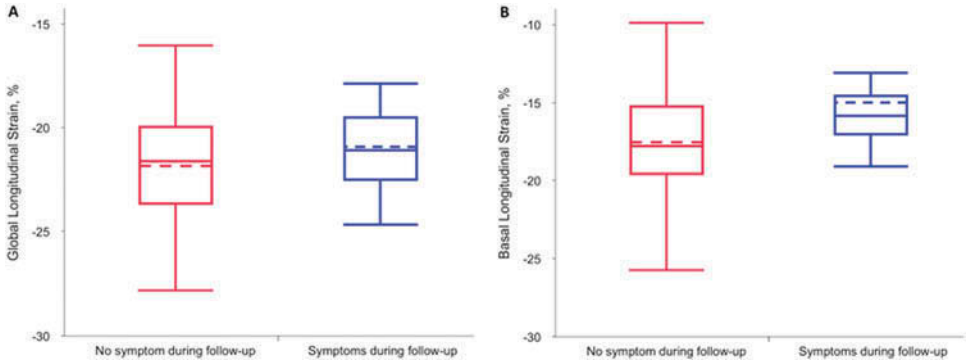

Figure 2. Comparisons of (A) global longitudinal strain values and (B) basal longitudinal strain values between patients who developed symptoms and those who did not. The box defines the interquartile range with the median indicated by the full line and the mean indicated by the dotted line.

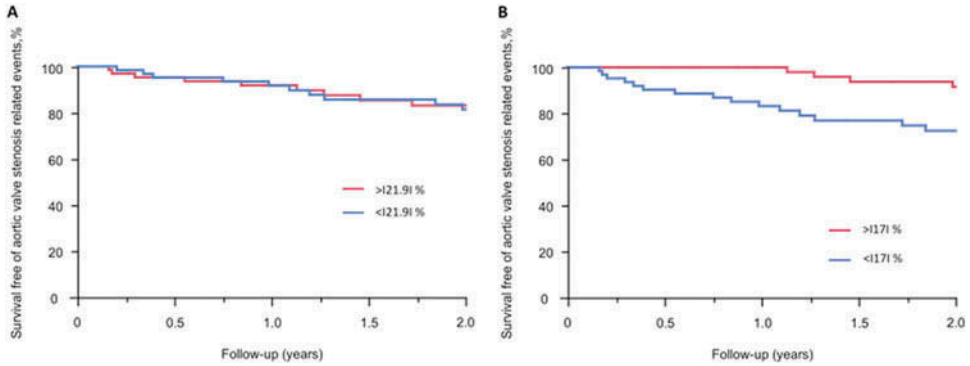

Figure 3. Survival free of aortic valve stenosis-related events (sudden death, congestive heart failure, or new AS-related onset of symptoms (dyspnea, angina or syncope)) by (A) median values of global longitudinal strain (below |21.9|% and above |21.9|%) and (B) median values of basal longitudinal strain (below |17|% and above |17|%).

Discussion

In this prospective cohort of asymptomatic patients with a wide range of AS severity and normal LVEF, unlike GLS, BLS was significantly correlated to AS severity and predicted the occurrence of AS-related events. However, overlap of BLS values between patients who developed symptoms and those who did not and similar BLS values at baseline and at the time of overt symptoms, raise the question regarding its use at an individual level.

Determinants of longitudinal strain

In our study of asymptomatic AS, determinants for GLS and BLS were different. GLS was associated with BMI but not with AS severity. A previous study described an association between excess abdominal visceral adipose tissue and lower GLS in AS patients [14] suggesting an inappropriate accumulation of lipids in cardiac myocytes leading to cell apoptosis.[15] Previous studies including ours,[5,8,16] report that GLS was significantly correlated to AS severity but it is important to mention that mainly symptomatic patients or with low LVEF were enrolled in these studies and an important overlap of GLS values between groups of AS severity was observed but often disregarded.

Unlike GLS, independent determinants of BLS were AS severity, heart rate and diastolic dysfunction. In line with the literature,[17] BLS declined with AS severity in contrast to GLS. During a cardiac cycle, the myocardial contraction is not homogeneous. It starts at the apex and shows significant delay in reaching the LV base. Therefore, basal segments are exposed to a higher afterload pressure during isovolumic contraction and may be the first to be impaired in AS.[18] Additionally, repetitive exposition of basal myocardium at an excess of pressure in patients with high heart rate can lead to BLS impairment. Finally, an association between diastolic dysfunction and BLS has also been previously reported[5] and highlights the fact that BLS is influenced by factors other than AS severity, especially in AS patients who are mostly elderly with comorbidities.

Prognostic value of longitudinal strain

In AS, LVEF impairment occurs late in the course of the disease. Identifying prognostic factors in asymptomatic patients with severe AS and preserved LVEF is an important clinical challenge and two-dimensional strain imaging is reputed to be more sensitive to ascertain LV myocardial contractility. In our study, GLS was not associated with symptoms-free survival contrasting with others trials. Looking at them attentively, GLS was predictive of all cause of death, cardiac death and major cardiac events but not specifically of AS-related events.[4,5,19,20] Nagata and colleagues[6] reported an incremental predictive value of both 3DGLS and 2DGLS for the occurrence of major cardiac events in 104 asymptomatic severe AS patients with preserved LVEF. However, only 3DGLS was an independent predictor in multivariate analysis whereas 2DGLS was not. In another group of 163 asymptomatic patients with an aortic valve area < 0.6 cm^2/m^2 and preserved LVEF, Lancellotti and co-workers[4] showed that GLS was associated to outcome but again end-points were not specific to AS and the clinical need of AVR was possibly biased by physicians' preference. Furthermore, GLS was the average of the segment strains from the apical four-chamber and two-chamber views and not from all the three apical views as recommended.[13]

In contrast, symptoms-free survival curves at 2 years according to median value of BLS were different and BLS was independently link to symptoms-free survival in the subset of patients with severe AS. Our results confirm those of Carstensen and colleagues[9] including 104 asymptomatic patients with moderate to severe AS where reduced BLS, but not GLS, was a significant predictor of indication for AVR and sudden cardiac death. However, although, BLS was significantly predictive of symptoms-free survival in our study, it is worth noting that there was an overlap of BLS values between patients who had an AS-related event and those who did not. Moreover, repeated BLS measurements at the time of the event were not different from baseline values. Our results may have important clinical implications. The wide overlap and the absence of significant changes when strain measurements were performed in patients who became symptomatic strongly suggest that clinical management should not rely on BLS, at least as a single parameter. BLS should be possibly integrated with other parameters and its prognostic value in combination with other parameters such as biomarkers, calcium scoring or AS progression rate deserve further evaluation.

Study limitations

First, our single center study included a limited number of severe AS with a relatively small number of AS-related events during the two years of follow-up. Nevertheless, the study was prospective with predefined intervals between visits with both simultaneous (same day) blinded clinical and echocardiographic assessment. In addition, outcome was assessed by experienced physicians unaware of the results of strain measurements and wide strain values have been observed but often disregarded in most previous studies. Nevertheless our results deserve confirmation in larger studies. Second, our population presented higher GLS and BLS values than previously reported in AS patients but our study included a wide range of age and AS severity. Third, GLS and BLS were re-measured again at the time of event in only nine patients and further confirmation would be of interest. Fourth, patients did not systematically undergo a stress test and the assessment of symptoms was based on self-reported exercise limitation. However, all patients were evaluated twice: first by the referring consultant and a second time by our team at the time of enrollment in the study. Finally, subclinical coronary artery disease could not be eliminated but all patients had normal EF and none had segmental wall motion abnormalities. Coronary angiography is recommended only as a preoperative test and thus, the present study reflects real-life practice.

Conclusion

In a prospective cohort of asymptomatic patients with a wide range of AS severity and normal LVEF, we showed that, in contrast to GLS, BLS was significantly correlated to AS severity and predictive of AS-related events in the subset of severe AS. However, overlap of BLS values between patients who developed symptoms and those who did not and the lack of BLS decrease at the time of occurrence of overt symptoms raise the question

regarding its use for management of asymptomatic AS patients at least as a single isolated parameter.

Acknowledgments

We would like to especially thank the team of the Centre d'Investigation Clinique, Christophe Aucan from the Assistance Publique – Hopitaux de Paris Département de la Recherche Clinique et du Développement and Estelle Marcault from the Unité de Recherche Clinique Paris Nord for their help and support during all these years.

Disclosure statement

Dr. Virginia Nguyen was supported by a grant from the Société Française de Cardiologie and the Fédération Française de Cardiologie; Dr. Melissopoulou was supported by a grant from the Association Citadelle Recherche et Formation – CHR de la Citadelle, Liège, Belgium. The COFRASA (clinicalTrial.gov number NCT 00338676) and GENERAC (clinicalTrial.gov number NCT00647088) studies are supported by grants from the Assistance Publique – Hôpitaux de Paris (PHRC National 2005 and 2010, and PHRC regional 2007). None of the authors has conflicts of interest or disclosures related to the present paper.

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