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Original Article

Severe Aortic Valve Stenosis: Symptoms, Biochemical Markers, and Global Longitudinal Strain

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Abstract

Background: According to the actual guidelines regarding severe aortic valve stenosis (AS), symptoms are the most important trigger for aortic valve replacement (AVR). However, the objective analysis of cardiological clinic can be confused, considering the aging population this disease affects and the comorbidities. **Objectives:** Looking for an objective marker of disease, useful for scheduling the correct AVR, we researched the relation between some biochemical markers of left ventricular (LV) dysfunction and its global longitudinal strain. **Materials and Methods:** We analyzed 74 consecutive patients (82 ± 4 years) with severe AS. We identified 61 patients with symptoms (angina, dyspnea, and syncope) and 13 asymptomatic patients. The clinical and echocardiographic parameters were compared between these two groups. LV ejection fraction (LVEF), LV global longitudinal strain (LVGLS), NT-pro-B-type brain natriuretic peptide (BNP), troponin T (TNT), creatine kinase-MB (CPK-MB), and myoglobin were determined at the time of evaluation. **Results:** Compared with the asymptomatic group, patients in the symptomatic group had a lower LVGLS ($P = 0.002$) and an increased pro-BNP ($P = 0.0002$). LVGLS showed a good correlation with pro-BNP as a marker of myocardial damage, with a linear increase of pro-BNP in patients with a linear decrease of LVGLS ($r = 0.43$). Despite the normal value of LVEF > 50% in asymptomatic patients, some of them (46%) have an early dysfunction of LVGLS. No other statistically significant difference emerged from the biochemical analysis, in TNT ($P = 0.29$), CPK-MB ($P = 0.36$), and myoglobin ($P = 0.38$). **Conclusions:** Pro-BNP and LVGLS can be considered an objective marker of clinical severity of AS disease, useful for management and scheduling of AVR, especially in asymptomatic patients.

Keywords: B-type natriuretic peptides, left ventricular global longitudinal strain, severe aortic valve stenosis

Introduction

Aortic valve stenosis (AS) is the most common valvular heart disease in Western countries. It affects almost 0.4% of the population and the prevalence increases with age, affecting almost 9.8% of people between the ages of 80 and 90 years.[1-3] Current guidelines recommend aortic valve replacement (AVR) for severe AS once symptoms occur or when there is ventricular systolic dysfunction.[4] The presence of significant AS in the absence of symptoms and normal left ventricular ejection fraction (LVEF) presents a clinical dilemma. The clinician must balance the risk of AVR with the risk of waiting for symptoms to develop. Prior studies have linked the severity of preoperative symptom status with worse postoperative outcomes.[5] It is increasingly being recognized that structural left ventricular (LV) changes, in the setting of significant AS, may not always be reversible even after successful valve intervention and may impact long-term survival, even in those with a normal LVEF. Thus, there is increasing interest in using sensitive markers of LV function, other than parameters derived from contractile function (LVEF), to determine outcomes in this population.[6-9] LV global longitudinal strain (LVGLS) is a quantitative measure for early LV dysfunction, enabling assessments of longitudinally oriented subendocardial myocardial fibers. Previous studies have found that brain natriuretic peptide (BNP) levels in patients with AS, correlate

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with the presence of symptoms, New York Heart Association class, and survival.[10-18] Hence, we aimed to describe the relationship between biochemical markers of myocardial damage and LVGLS in patients with different symptoms and despite the clinical assessments and the LVEF, identify patients with reduced contractility that can benefit from a closer follow-up or AVR.

Materials and Methods

Patient population

Between February 2017 and February 2018, 74 patients (82 ± 4 years) referred to our center with severe aortic stenosis were evaluated by our echocardiographic laboratory and prospectively enrolled in this study. Symptoms related to AS were recorded by a cardiologist at admission and after echocardiographic evaluation. All patients had severe aortic stenosis (aortic valve area [AVA] ≤1 cm^2 or indexed AVA ≤0.6 cm^2/m^2 of body surface area (BSA), P_{med} transvalvular ≥40 mmHg and V_{max} >4 m/s).

The whole population was divided into two groups according to symptoms: 61 patients characterized by, at least one of the following symptoms: syncope, stable or instable angina, and dyspnea; 13 patients with severe AS but without symptoms. We excluded people with severe AS and other cardiac or respiratory comorbidities confounding the aortic clinic and people with more than moderate mitral insufficiency, as assessed by color Doppler imaging. Other data collected at the time of admission included the cardiovascular risk factors, previous history of renal injury, stroke, previous coronary artery disease, and presence of atrial fibrillation (AF). Concerning the biochemical markers, we required a blood test of each patient from the laboratory of our hospital, analyzing myoglobin (ng/mL), creatine kinase-MB (CPK-MB) (Ui/L) and troponin (ng/L), and pro-BNP (pg/mL) as markers of LV function. Pathological values of pro-BNP ≥100 pg/mL, troponin ≥40 ng/L, CPK-MB ≥5.2 Ui/L, and myoglobin ≥20 ng/mL were taken into consideration.

Data collection and definitions

All patients have been submitted to cardiologic visit and transthoracic echocardiography, done with Epiq 7 Philips echocardiography and bi-tridimensional ultrasound. Each ultrasound measurement was taken following the guidelines of the American Society of Echocardiography and European Association of Cardiovascular Imaging (EACVI).[17] LV volumes and ejection fraction (EF) were calculated using the biplane Simpson disk method. LV mass was estimated using the linear method with the formula recommended by the American Society of Echocardiography and indexed for BSA (cutoff value for hypertrophy >115 g/m^2 for men and >95 g/m^2 for women). Continuous-wave Doppler was used to measure the aortic transvalvular peak velocities; peak and mean gradients were calculated using the simplified Bernoulli equation and AVA using the continuity equation (AVA: $A_{LV\ outflow\ tract\ (LVOT)} \times VTI_{LVOT}/VTI_{AV}$). Valvular insufficiencies were assessed by color Doppler imaging. In order to correct the limitations of AVA derived by Doppler echocardiography and continuity equation, we assessed the EF/velocity ratio (EFVR) with the following formula: EFVR: LVEF/(4 × V^2), with a pathological value <0.9 s^2 m^2. The diameter of LVOT was measured using parasternal long-axis projection.

We calculated the LV relative wall thickness (RWT) with the formula: (IVS + PWT)/LVID, with a normal range of 0.32–0.42, and the LV end-diastolic volume indexed for BSA (LV end-diastolic volume indexed [LVVi]), with normal cutoff of 75 mL/m^2. According to the classical hypertrophy categories, we considered:

- Normal: Ventricle with LV indexed mass <95/115 g/m^2 and RWT <0.42
- Concentric remodeling: LV indexed mass <95/115 g/m^2 and RWT >0.42
- Concentric hypertrophy: LV indexed mass >95/115 g/m^2 and RWT >0.42
- Eccentric hypertrophy: LV indexed mass >95/115 g/m^2 and RWT <0.42.

According to the new hypertrophy categories, we considered:

- Normal ventricle: LV indexed mass <95/115 g/m^2, RWT <0.42, LVVi <75 mL/m^2
- Eccentric hypertrophy: LV indexed mass > 95/115 g/m^2, RWT <0.42, LVVi <75 mL/m^2
- Concentric hypertrophy: LV indexed mass >95/115 g/m^2, RWT >0.42, LVVi <75 mL/m^2
- Mixed hypertrophy: LV indexed mass >95/115 g/m^2, RWT >0.42, LVVi >75 mL/m^2
- Concentric remodeling: LV indexed mass <95/115 g/m^2, RWT >0.42, LVVi >75 mL/m^2
- Eccentric remodeling: LV indexed mass <95/115 g/m^2, RWT <0.42, LVVi >75 mL/m^2
- Dilated hypertrophy: LV indexed mass >95/115 g/m^2, RWT <0.42, LVVi >75 mL/m^2
- Unclassified includes patients with a combination of variables that cannot be categorized.

LVGLS was evaluated as the average of the segment strains from the apical four-chamber, two-chamber, and long-axis views. The endocardium was manually traced in each view, and the region of interest width was adjusted to include the entire myocardium. Myocardial motion was tracked by automated software, and only segments with adequate tracking were accepted for further analysis. In each echographic project, the myocardium profile has been divided into the following six regions: inferior, infero-septal, antero-septal, anterior, antero-lateral, and infero-lateral, analyzed with speckle-tracking technique. First, the LV peak systolic longitudinal strain (LV PSLS) was calculated, taking into consideration the maximum negative value of LV wall deformation during the ejective period, from the beginning QRS to the aortic valve closure. Using the average of the LV PSLS of these projections, we calculated the LVGLS. GLS is

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a negative parameter, and less negative values represent lesser degrees of contraction. For outcome analysis, GLS near 20% has been considered normal; the more it increases, the more it has been considered pathologic.

Statistical analysis

Categorical and dichotomous variables were presented as counts and percentages and were compared by Chi-square test or Fisher's exact test, as appropriate. Continuous variables were presented as mean ± standard deviation or median (interquartile range) based on their distribution. Unpaired Student's *t*-tests were used to compare continuous parameters following a normal distribution, whereas Mann–Whitney *U*-tests were used to compare continuous variables with skewed distribution. Categorical and dichotomous variables were presented as counts and percentages and were compared by Chi-square test or Fisher's exact test, as appropriate. $P = 0.05$ was set for significance. The correlation was analyzed using the Pearson's method and simple linear regression with 95% confidence interval and showed as r^2. All data were processed using the Statistical Package for the Social Sciences version 21 (SPSS Inc., version 21, Chicago, IL, USA).

Results

Patient characteristics

Demographic and clinical characteristics of the study population are presented in Table 1. The mean age of the patients was 82 ± 4 years, and 45.9% of the patients were male. Twenty-three percent of the population, represented by 17 patients, had an acute myocardial infarct in anamnesis, treated with percutaneous transluminal coronary angioplasty at least 3 years before the analysis; six patients (8.1%) had a previous heart surgery. Concerning symptoms, out of the 61 patients composing the symptomatic cohort, eight of them (13.1%) had syncope; seven patients (11.5%) had stable angina, and 7 others had instable angina. Dyspnea, present in sixty patients of this group (98.4%), has been the most represented symptom during the analysis [Figure 1].

Echocardiographic and biochemical characteristics

Echocardiographic characteristics are shown in Table 2. AVA average was comparable in both groups ($P = 0.36$). The same happened for ΔP_{max} (83.9 ± 22.6 mmHg vs. 81 ± 27.4 mmHg, $P = 0.72$) and ΔP_{med} (52.7 ± 15.1 mmHg vs. 51.4 ± 20.4 mmHg, $P = 0.83$). During the analysis, a moderate mitral insufficiency was present in 27 symptomatic and 6 asymptomatic patients (44%); moderate tricuspidal insufficiency was observed in 21 patients (28%), of which only one was asymptomatic; 9 symptomatic patients (13,3%) had a moderate aortic valve insufficiency, vs nobody of asymptomatic group (−13.7% ± 4.4% vs. −17.1% ± 4.3%, $P = 0.02$).

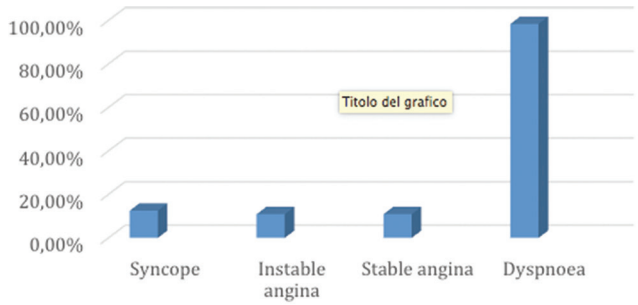

Figure 1: Previous symptoms in symptomatic patients (%)

Table 1: Population characteristics

	Study population (*n*=74)	Symptomatic patients (*n*=61)	Asymptomatic patients (*n*=13)
Age, years±SD	82±4	82±5	82±3
Male, *n* (%)	34 (45.9)	27 (44.3)	7 (53,8)
CV risk factors, *n* (%)			
Hypertension	65 (87.8)	54 (88.5)	11 (84.6)
Diabetes	19 (25.7)	12 (19.6)	7 (53.8)
Dyslipidemia	33 (44.6)	29 (47.5)	4 (30.7)
Smoking	16 (21.6)	14 (22.9)	2 (15.3)
Anamnesis, *n* (%)			
NYHA≥3	50 (67.5)	50 (83.6)	/
Kidney's failure	29 (39.2)	29 (47.5)	/
Previous CABG	6 (8.1)	6 (9.84)	/
PTCA	17 (23)	14 (23)	3 (23)
Previous AMI	16 (21.6)	14 (23)	3 (23)
Previous TIA	5 (6.8)	5 (8.2)	/
Previous ICTUS	1 (1.4)	1 (1.6)	/
Heart failure	13 (17.6)	13 (21.3)	/
PM patients	8 (10.8)	7 (11.4)	1 (7.7)
Atrial fibrillation	11 (14.9)	11 (18)	/

CABG=Coronary artery bypass grafting, CV=Cardiovascular, NYHA=New York Heart Association, MI=Myocardial infarction, PTCA=Percutaneous transluminal coronary angioplasty, TIA=Transient ischemic attack, PM=Pacemaker, SD=Standard deviation, /=Zero Patients

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Regarding the mitral insufficiency, we did not have any patient with severe mitral insufficiency; the mean E peak for symptomatic patients was 91.78 (±33) versus 98.3 (±40) in the other group ($P = 0.6$).

LVEF, calculated with Sympson's formula, resulted comparable in both groups, with an average of 56.3% in symptomatic patients and 60% in the others, $P = 0.09$.

Another statistically significant difference emerged from the comparison of pro-BNP value in the two groups, with an increased value in the symptomatic patients (1649 ± 289 pg/mL), compared to the others (354 ± 692 pg/mL, $P = 0.002$).

No other significant difference emerged from the biochemical analysis, for the troponin, CPK-MB, and myoglobin markers [Table 3].

We assessed the EFVR for each group of the study's population, with the following, not statistically significant, result: 48 (79%) of the symptomatic patients had an EFVR < 0.90 s^2 m^2, versus 8 (61.5%) of asymptomatic population ($P = 0.13$); the mean of EFVR in symptomatic population was 0.72 s^2 m^2 (±0.23) versus 0.83 s^2 m^2 (±0.32) in the other group ($P = 0.24$).

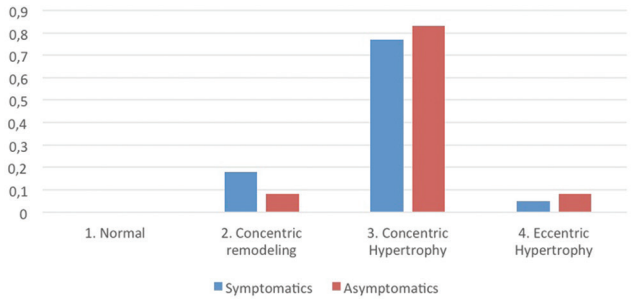

Figure 2: Four classical hypertrophy category distribution (%)

According to the LV indexed mass, RWT, and LVVi, there was no significant difference between the study groups: the mean LV indexed mass was 139.23 g/m^2 (±30.38) in the symptomatic group versus 135.41 g/m^2 (±27.02) in the other group ($P = 0.66$); the symptomatic mean RWT was 0.56 (±0.1) versus 0.53 (±0.1) in the asymptomatic group ($P = 0.56$); LVVi was 57.05 mL/m^2 (±19.46) in the symptomatic group versus 50.18 mL/m^2 (±10.57) in the other group ($P = 0.10$). We have also calculated the distribution of our population in the different hypertrophy classes, considering the classical four categories and the new eight, with the following, not statistically significant, results:

Regarding the four-class distribution, we did not have any patient in both groups with a normal ventricle [Figure 2]:

- Concentric remodeling: 18% (11) of the symptomatic patients versus 15% (2) of the other group
- Concentric hypertrophy: 77% (47) of symptomatics versus 76% (10) of asymptomatics
- Eccentric hypertrophy: 5% (3) of symptomatics versus 8% (1) of asymptomatics.

Regarding the eight-class distribution, we did not have any patient in both groups with a normal ventricle [Figure 3]:

- Concentric hypertrophy: 65.5% (40) of symptomatics versus 76% (10) of asymptomatics

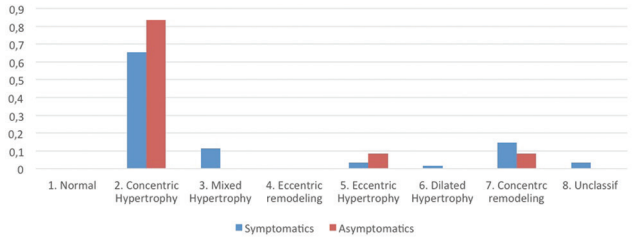

Figure 3: Eight new hypertrophy category distribution (%)

Table 2: Echocardiographic characteristics

	Study population ($n=74$)	Symptomatic patients ($n=61$)	Asymptomatic patients ($n=13$)	*P*
LVEF (%)	56.3±10.6	56.3±9.7	60±6	0.09
Mass LV (g/m^2)	137.2±31.8	139.2±30.3	135.4±27	0.67
LVEDV, mean±SD	95.2±34.1	97.2±35.6	91.1±24.9	0.48
LVESV, mean±SD	42.1±24.1	43.5±25.9	36.5±14.2	0.20
LAVi (ml/mq), mean±SD	46.5±17.6	45.4±17.6	53.7±16.1	0.13
PAPs (mmHg), mean±SD	40.7±15.6	42.1±15.6	35.8±14.4	0.19
Moderate/severe TI, *n* (%)	21 (28)	19 (31)	2 (15.3)	0.32
Moderate/severe MI, *n* (%)	33 (44)	27 (42)	6 (46)	1
Moderate/severe AoI, *n* (%)	9 (13.3)	9 (14)	0 (0)	0.34
ΔPmax (mmHg), mean±SD	82.6±24.1	83.9±22.6	81±27.4	0.72
ΔPmed (mmHg), mean±SD	51.9±16.3	52.7±15.1	51.4±20.4	0.83
AVA (cm^2), mean±SD	0.62±0.2	0.63±0.2	0.67±0.2	0.36
Stroke volume (ml), mean±SD	70.4±20.1	70.2±20.5	73.2±14.9	0.63
Sm TDI wave (cm/s), mean±SD	5.5±1.4	5.52±1.4	5.8±0.5	0.21
LV global longitudinal strain (%), mean±SD	−14.1±5.0	−13.7±4.47	−17.1±4.3	0.02

LV=Left ventricular, LVEF=LV ejection fraction, LVEDV=LV end-diastolic volume, LVESV=LV end-systolic volume, LAVi=Indexed left atrium volume, PAPs=Systolic pulmonary artery pressure, TI=Tricuspidalic insufficiency, MI=Mitral insufficiency, AoI=Aortic valve insufficiency, AVA=Aortic valve area, TDI=Tissue Doppler imaging, SD=Standard deviation

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- Mixed hypertrophy: 11.4% (7) of symptomatics versus 0 asymptomatics
- Eccentric remodeling: None of the groups
- Eccentric hypertrophy: 3.3% (2) of symptomatics versus 8% (1) of asymptomatics
- Dilated hypertrophy: 1.6% (1) of symptomatics versus 0 asymptomatics
- Concentric remodeling: 14.7% (9) of symptomatics versus 15% (2) of asymptomatics
- Unclassified: 3.3% (2) symptomatics versus 0 asymptomatics.

Concerning the LVGLS, approximately 78% of the symptomatic patients and 46% of asymptomatic patients had a pathological value of strain ($P = 0.006$) and regarding the pro-BNP, 87% of symptomatic and 45% of asymptomatic patients had a pathological value ($P = 0.01$).

With regard to the relationship between LVGLS and pro-BNP, the more the LVGLS became worse, the more the pro-BNP increased, following a linear progression in both groups ($r = 0.43$) [Figures 4-6].

We have also related the value of LV-GLS with the different LV mass class distribution, in both groups, but we did not find any statistically significant result ($P = 0.81$).

With reference to the analysis of valvular insufficiencies, no statistically significant difference emerged between the two groups, for mitral ($P = 0.8$), tricuspidalic ($P = 0.6$), and aortic valve insufficiency ($P = 0.8$). When comparing the LVGLS with the severity of these valvular insufficiencies, no significant importance emerged ($r < 0.01$) [Figure 7].

Discussion

Our observational study showed:

1. A significant difference of LVGLS and pro-BNP between symptomatic and asymptomatic patients, with an increasing value of Pro-BNP and a decreasing longitudinal function in the first group
2. A linear relation between LVGLS and Pro-BNP in both groups that, the more the first decreases, the more the second increases.

A worse value of LVGLS in symptomatic patients can be related to a progressive loss of LV longitudinal fiber function and consequently, the beginning of symptoms. Considering the preserved EF, the echographic speckle-tracking technique showed a reduced longitudinal systolic function in symptomatic groups. This function, still preserved in asymptomatic patients, can guarantee a better integrity of the LV itself and delay the probability of the symptomatology's beginning. This agrees with the actual literature,[17-20] where the prognostic value of LVGLS in patients with severe AS has been proven. Reduced

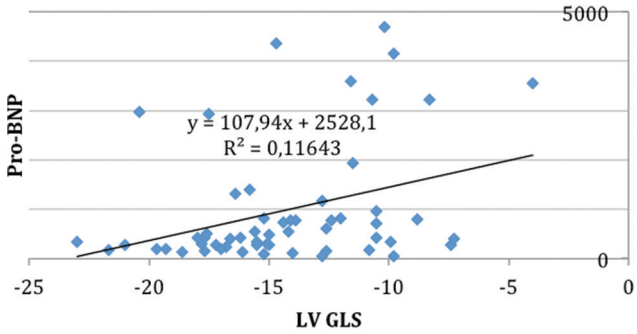

Figure 4: Relation between LVGLS and pro-BNP in symptomatic patients. BNP = B-type natriuretic peptide, LVGLS = Left ventricular global longitudinal strain

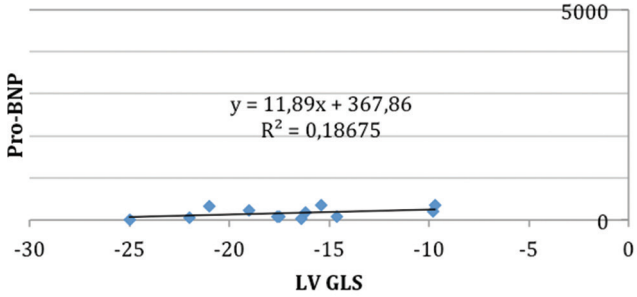

Figure 5: Relation between LVGLS and pro-BNP in asymptomatic patients. BNP = B-type natriuretic peptide, LVGLS = Left ventricular global longitudinal strain

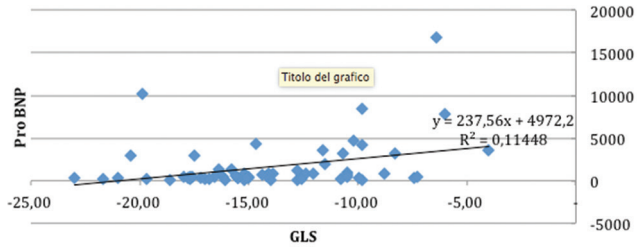

Figure 6: Relation between LVGLS and pro-BNP in the study population. BNP = B-type natriuretic peptide, LVGLS = Left ventricular global longitudinal strain

Table 3: Biochemical characteristics

	Study population ($n=74$)	Symptomatic patients ($n=61$)	Asymptomatic patients ($n=13$)	*P*
Pro-BNP (pg/ml), mean±SD	1441±2652	1649±2896	354.7±692	0.002
CPK-MB (Ui/L), mean±SD	6.28±11.2	5.3±9	13.8±22.9	0.367
Troponin (ng/L), mean±SD	93.1±268.7	100.4±288.2	15±21.5	0.293
Myoglobin (ng/ml), mean±SD	55.4±29.4	56.9±30.3	45.9±23.8	0.380

SD=Standard deviation, BNP=B-type natriuretic peptide, CPK-MB=Creatine kinase-MB

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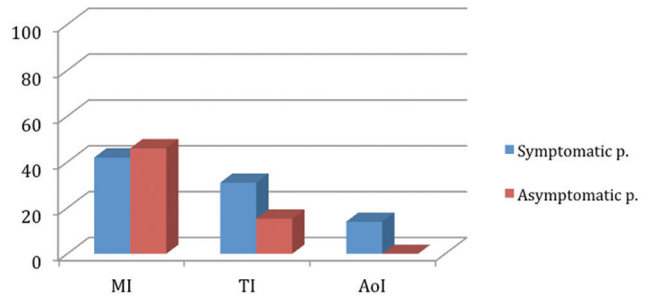

Figure 7: Valvular insufficiencies in both groups. AoI = Aortic valve insufficiency, MI = Mitral insufficiency, TI = Tricuspidalic insufficiency

value of deformation and speed longitudinal contraction shown in severe AS patients can be related to structural and functional myocardial alteration, caused by the expression of high-weight myosin chain, the depositing amorphous and noncontracting mass, and insulin-like growth factor-1 myocardial resistance. The progressive collagen deposit in subendocardial myocardial fibers can cause a reduced longitudinal strain rate.[9,21-23] The continuous worsening of LVEF, caused by the lasting attempt at compensation, is related to a reduction of survival and to a worse outcome after AVR. Although this is not a prospective study on the survival of AS patients, we found a significant difference of LVGLS in two different moments of the same disease, placed in continuum of each other.

The same was found regarding pro-BNP, an increase in patients with advanced and symptomatic AS. Different studies[11,24-28] have presented the relation between B-type natriuretic peptide and the amount of LV fibrosis and myocardial dysfunction. We sought its importance during the management of patients with severe AS and found that it can be helpful in cases of LV-compromised longitudinal function and asymptomatic patients or, in symptomatic patients in the case of many confounding comorbidities. Considering the discussed prognostic value of LVGLS and pro-BNP in severe AS, their role is even increased during the evaluation of patients with no clear heart disease symptoms or, in the case of comorbidities. During our evaluation, 45% of the asymptomatic patients showed values of pro-BNP and LVGLS to be previously altered, compared to normal levels. Reduced LVGLS can predict an early and still, asymptomatic LV systolic dysfunction that, though not shown, can compromise long-term survival. The same regarding pro-BNP, a previous increase, can lead to a precocious clinical worsening.

We found a linear decreased LVGLS and increased pro-BNP in both groups. Presently, there is no study confirming the clinical value of this relation and its pathogenetical origin. Goodman *et al.*,[29] in 2016, led a prospective study with the aim of evaluating the prognostic value of both variables in patients with severe AS and they proved the correct relation between a worsening LVGLS, an increasing pro-BNP, and the worse survival of these patients. However, they recognized the better value of worsening LVGLS to detect an early systolic myocardial dysfunction, rather than pro-BNP. This result can be related with the evidence of some asymptomatic patients that, even presenting normal values of pro-BNP, show a previous longitudinal dysfunction. Considering the reduced sample of asymptomatic patients analyzed, it can be difficult to assert such an important result, so it is proposed to investigate better in this field.

In this study, the LVGLS resulted independent from LV mass, disaccording with previous studies in literature[19] where, instead, longitudinal systole function is related to the LV hypertrophy and geometry. Even this result can be caused by the reduced sample of patients.

However, according to literature, we found an independent relationship between LVGLS and LVEF as markers of LV systolic function. Analyzing patients heterogeneous for symptoms but homogeneous for EF (LVEF >50%) we had a significant difference of LVGLS. According to literature, LVGLS showed a better capacity of detecting LV systolic dysfunction, therefore we can confirm its value during the management of patients with severe AS. It can be better shown by a prospective study analyzing the follow-up of asymptomatic patients, able to find its realistic role in the developing pathology. Only a follow-up program, evaluating pro-BNP, LVGLS, and symptoms, can detect patients that, even asymptomatic, may benefit from an early percutaneous or surgical AVR.

Considering the other biochemical markers, troponin, myoglobin, and CPK MB do not share the prognostic value of pro BNP as a quantitative marker of survival and severity of patients with AS [30], No significant difference emerged from the comparison between the two groups, according to previous studies in literature,[29] showing any utility in AS management.

Furthermore, we assessed the EFVR ratio, a simple function-corrected index of AS severity, which is used to overcome the limitations of AVA derived by echoDoppler and continuity equation. In fact, according to a recent study,[31] EFVR showed a good diagnostic accuracy in identifying effective orifice area under 1 cm^2 in patients with severe AS, according to AVA measured using Gorlin formula during cardiac catheterization, and a good capacity to reduce error related to echocardiographic measurements. Moreover, these authors showed that EFVR predicts adverse outcomes in terms of cardiac mortality or AVR, especially in asymptomatic patients with severe AS. In our study, we did not find any significant difference of EFVR between the two populations, a sign of homogeneity of the groups. Despite this, a reduced value of EFVR even in asymptomatic population can underline the severity of the valvular disease in the population and therefore, its role in the evaluation of a patient with severe AS, especially without symptoms. Even this value may be shown in a prospective follow-up study.

According to the LV mass, we have evaluated our study population with the classical EACVI four-class hypertrophy distribution and even the new Gaasch–Zile eight-class

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distribution. In fact, according to Di Nora *et al*.'s study,[32] assessing the remodeling/hypertrophy patterns in patients affected by aortic stenosis, especially asymptomatic patients with severe AS, is an important step during the evaluation because its impact on prognosis is crucial. The new eight-class distribution, with the evaluation of LVVi, has recently shown a better prognostic stratification, compared with the four-class one, with heart failure stages A and B. The majority of our study population had a concentric hypertrophy in both groups (65.5% vs. 83.3%) and concentric remodeling (14.7% vs. 8.3%), and this correlates very well with other literature's findings. In fact, the afterload caused by severe aortic stenosis causes an increase of contractile elements of the myocardium, resulting in a LV remodeling that leads to a concentric hypertrophy, in order to preserve cardiac output, but this excessive LV remodeling process becomes maladaptive, leading to a diastolic, and then systolic dysfunction. Unfortunately, our study did not evaluate the prognostic value of these hypertrophy classes, but showed a homogeneity even for these variables of the population. We tried to correlate the LV mass with the LV-GLS, considering that this variable is linked with the myocardial thickness, but we did not find any statistical correlation. Maybe a study with more patients can clear this doubt.

In symptomatic population, we included 11 people (14%) with permanent AF, diagnosticated at least 1.5 years before our evaluation, with oral anticoagulant and other medical optimized therapy. We did not include people with acute heart failure and AF re-acutizzation or onset, in order to exclude a confounding clinical factor. In fact, according to different studies,[33] AF or other cardiac arrhythmias can be a cause of decompensation of severe AS patient, with a pure prognostic value.

Analyzing valvular insufficiencies, both groups resulted homogeneous values for mitral valve insufficiency, without any significant difference for patients with moderate-grade disease. As for tricuspidal valve insufficiency, considering the presence of symptomatic patients with a moderate-to-severe valvular insufficiency, no significant difference emerged during the evaluation of LVGLS and pro-BNP. Considering aortic valve insufficiency, the reduced sample of asymptomatic patients did not allow a correct evaluation of this relationship. In patients with a moderate-to-severe mitral valve insufficiency, the values of LVGLS and ProBNP did not show any relationship with the other valvular diseases, but, according to literature, the reduced sample can not prove a real independence of the variables.

Study limitations

Of course, several limitations should be considered inherent to our study, by the virtue of its observational nature. Intentionally, we did not exclude patients with coronary artery disease from the analysis, with the hypothesis of possible independent contribution to LV systolic/diastolic dysfunction and thus to symptoms. We also included, in the symptomatic population, few patients with permanent AF, diagnosticated at least 1.5 years before our evaluation, without a comparison with asymptomatic people with permanent AF, considering this arrhythmia not to be a cause of cardiac decompensation.

Our study was conducted in a single referral hospital, and therefore relatively few patients with isolated severe AS without comorbidities were included.

Finally, the present study should be considered as hypothesis generating, and clearly, larger multicentric studies are needed to confirm these exploratory results.

Conclusions

There is a linear relation between GLS, pro-BNP, and symptoms of aortic stenosis.

This supports the concept of transition from adaptive LV remodeling to myocyte death as an important determinant of symptoms. Concerning asymptomatic patients with previous longitudinal systolic dysfunction and preserved LVEF, LVGLS raises particular importance to detect any precocious LV dysfunction and identify patients that can benefit from a closer follow-up or AVR.

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Conflicts of interest

There are no conflicts of interest.

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