

# Severe aortic stenosis with preserved ejection fraction and evidence of impairment in structure, myocardial strain and ventricular function: A new contribution to clinical decision making

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## Abstract

**Background:** *Left ventricular ejection fraction (LVEF) is among the parameters that are usually employed to define surgical timing of severe aortic stenosis (AS). Our hypothesis states that even when their LVEF is preserved, patients with severe symptomatic AS have impaired myocardial structure and function, and such impairment is related to the deleterious progression of left ventricular hypertrophy (LVH) from the compensated to the decompensated stage, as shown by the changes in diastolic function and the increase in left ventricular end-diastolic pressure (LVEDP).*

**Methods and Results:** *A total of 26 patients with severe AS and LVEF > 50% referred for aortic valve replacement underwent catheterization, echocardiography and an intraoperative biopsy. Patients with severe symptomatic AS were classified as: group 1 (G1; compensated LVH, LVEDP < 15 mm Hg without coronary artery disease [CAD], n = 7), group 2a (G2a, decompensated LVH, without CAD, n = 7), and group 2b (G2b, decompensated LVH with CAD, n = 12). Differences were seen in the following: myocyte area [ $\mu\text{m}^2$ ]: G1:  $328 \pm 66$ , G2a:  $376 \pm 22$ , G2b:  $385 \pm 13$ ,  $p < 0.01$ ; collagen volume [%]: G1:  $4.77 \pm 1.27$ , G2a:  $8.40 \pm 1.27$ , G2b:  $11.05 \pm 3.08$ ,  $p < 0.01$ ; LVEDP normalized by diastolic diameter [mm Hg/mm]: G1:  $0.27 \pm 0.01$ , G2a:  $0.39 \pm 0.06$ , G2b:  $0.44 \pm 0.11$ ,  $p < 0.02$ ;  $+dP/dt_{max}/LVEDP$  [mm Hg/s/mm Hg]: G1:  $176 \pm 45$ , G2a:  $89.6 \pm 20$ , G2b:  $113.1 \pm 41$ ,  $p < 0.01$ ; two-dimensional peak systolic longitudinal strain [%]: G1:  $-17.7 \pm 4.75$ , G2a:  $-13.4 \pm 3.04$ , G2b:  $-13.5 \pm 3.13$ ,  $p < 0.05$ .*

**Conclusions:** *Patients with severe symptomatic AS and preserved ejection fraction who develop decompensated LVH characterized by increased LVEDP, exhibit an abnormal myocardial structure and diastolic and systolic impairment. (Cardiol J 2015; 22, 6: 613–621)*

**Key words:** aortic stenosis, hypertrophy, function

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Received: 06.05.2015

Accepted: 23.05.2015

## Introduction

Management of patients with severe aortic stenosis and preserved ejection fraction (EF) is still controverted and the decision of whether to “watch and see” vs. early intervention remains debatable [1–3].

Current guidelines determine surgical timing according to symptoms and impairment of systolic function, defined by an EF below 50% [4, 5]. Notwithstanding, some patients operated according to that criterion will have a poor outcome in the long-term follow-up, demonstrating that in fact, EF may not be sensitive enough to be used as a cutoff point and prognostic marker [6, 7].

The presence of fibrosis and myocyte changes together with an elevation in left ventricular (LV) end-diastolic pressure (LVEDP) or systolic function impairment reduce postoperative survival [8–11]. Hence, it could be useful to detect myocardial impairment in order to make therapeutic decisions before actual myocardial damage occurs. Along these lines, the use of new indices may help to identify such changes and define high risk populations that might benefit from an early surgical intervention [12].

Imaging with two-dimensional (2D) strain has been shown to be an appropriate method to assess myocardial contractility, as well as structure, and could be used to detect changes in LV performance [13, 14].

We hypothesize that in patients with severe symptomatic aortic stenosis (AS), even in the presence of a preserved EF, myocardial function and structure are impaired, and such impairment is related to the progression of LV hypertrophy (LVH), from the compensated to the decompensated stage, manifested by an increase in LVEDP.

In this study, we evaluated patients with severe symptomatic AS (SSAS) and preserved EF with the purpose of: a) detecting changes in LV systolic and diastolic function and their correlation with changes in myocardial structure, that could allow to discriminate different stages of progression of LVH, as assessed by LVEDP; b) analyzing 2D peak systolic longitudinal strain, preoperatively and 1 year after the aortic valve replacement, in agreement with de preoperative LVEDP values.

## Methods

### Study population

We prospectively included 26 consecutive patients (age:  $67 \pm 11$  years, 53% male), with SSAS

(defined by symptoms such as angina, syncope or dyspnea occurring at rest or with exercise) and by Doppler echocardiography (valve area  $< 1 \text{ cm}^2$ , mean gradient  $> 40 \text{ mm Hg}$ ) and an EF  $> 50\%$ , referred to the Hospital Universitario Austral for aortic valve replacement. Prior to surgery, all patients underwent cardiac catheterization and Doppler echocardiography, and during valve replacement surgery a biopsy was obtained from the LV anterolateral wall. At 1 year post valve replacement, a new echocardiogram was performed. Patients with cardiomyopathy or other concomitant valve diseases were excluded. All patients accepted to participate in the study by signing an informed consent form (approved according to the Ethics Committee guidelines of the Hospital Universitario Austral) and the Declaration of Helsinki (1975). Patients with SSAS were divided into three groups according to their LVEDP ( $<$  or  $\geq 15 \text{ mm Hg}$ ) [15] and patients with a LVEDP  $\geq 15 \text{ mm Hg}$  were further categorized according to the presence of coronary artery disease (CAD) (lesion in one coronary artery with obstruction  $\geq 50\%$ ): group 1 (G1; compensated LVH, LVEDP  $< 15 \text{ mm Hg}$  without CAD,  $n = 7$ ), group 2a (G2a, decompensated LVH without CAD,  $n = 7$ ), group 2b (G2b, decompensated LVH with CAD,  $n = 12$ ).

### Study protocol

Echocardiography was performed with assessment of 2D peak systolic global longitudinal strain (SGLS) by speckle tracking technique, using Vingmed VIVID 7 equipment (GE Vingmed, Milwaukee, WI, USA) with a 3.5 MHz transducer; measurements were performed according to recommendations of the American Society of Echocardiography (ASE) [16]. The following variables were calculated: LV fractional shortening, LV volume, EF (using Simpson’s method) [16], and midwall fractional shortening (MFS) [17] which was normalized by end-systolic meridional stress [18]. Aortic valve area was calculated using the continuity equation and gradients with the modified Bernoulli equation ( $4V^2$ ). Left ventricular mass (LVM) was calculated according to the ASE guidelines, and normalized by body surface to obtain the LVM index (LVMI); values were considered high when they exceeded  $115 \text{ g/m}^2$  in men and  $95 \text{ g/m}^2$  in women [19].

Assessment of 2D peak SGLS (%) of the LV was performed with 2D echocardiography and grey scale speckle tracking imaging, using 2-, 3-, and 4-chamber views from the apical long axis, and a frame rate  $> 50$  frames/s [20]. The Lagrange formula ( $L2L_0/L_0$ ) was used to calculate percent strain [21]. Strain was quan-

tified using GE software (EchoPAC, version 7.0.0, General Electric Vingmed). The endocardial contour was traced manually at end-systole; subsequently the software automatically traced the region of interest concentrically [22]. For strain analysis, each apical view was divided into 6 segments and SGLS was then calculated from the average of 18 segments.

### Catheterization

A LV catheterization was performed prior to surgery to record LV pressure and the aortic/LV gradient, which were recorded with a computer-assisted system (Philips XPER (XIM) Xper Information System (XIMs) Polygraph, version 1.2.0.1474), connected to an Edwards Life Science pressure transducer. The following pressures were measured: aortic pressure, LV systolic pressure [mm Hg] and LVEDP [mm Hg]; the following indices were also calculated: maximal rate of rise in LV pressure ( $+dP/dt_{max}$  [mm Hg/s]), the inverse slope of the line which results from applying the Ln to the equation of exponential drop in LV pressure during the isovolumic relaxation period (linear tau [ms]), and the time elapsed since LV pressure drops to 50% of its initial value ( $t_{50}$ ), considering as initial LV pressure the value corresponding to  $-dP/dt_{max}$ .

The contractility index was calculated as the ratio between maximal rate of rise in LV pressure ( $+dP/dt_{max}$  [mm Hg/s]) normalized by LVEDP [23].

The two components of diastolic function were evaluated: myocardial relaxation and myocardial chamber stiffness. To evaluate myocardial chamber stiffness we calculated the ratio between LV pressure and LV end-diastolic diameter. In order to assess the catheter sensitivity, the recording of ventricular pressure of the conventional catheter was compared in 3 patients with that obtained by a catheter tip transducer (Millar Instruments Inc.) that prevents potential problems caused by the fluid filled catheter. We observed that both the rise and decay slopes of the ventricular pressure were similar, therefore no differences were found in the measurements of the relaxation variables. As expected, measurements of the systolic and diastolic pressures were similar with both catheters.

### Histomorphometric analysis

Myocardial biopsies of the LV free wall were obtained during aortic valve replacement procedures. Tissue samples were fixed in 10% buffered formalin at room temperature and paraffin-embedded; subsequently, 5  $\mu$ m serial sections

were obtained and stained with hematoxylin and eosin, Picrosirius red and rhodamine-conjugated lectin (WGA# RL-1022, Vector Laboratories, Burlingame, CA).

Myocyte cross-sectional area was determined on digitized images of rhodamine-conjugated lectin-staining; such images were obtained using a fluorescence microscope (Olympus BX61) attached to a digital camera and connected to a computer equipped with image analysis software. Myocytes' outlines were traced and cell areas measured with Image-Pro Plus 6.0 (Media Cybernetics, Inc., Silver Spring, Md). At least 80 measurable cross sections of myocytes were routinely measured [24]. In the slices stained with Picrosirius red, interstitial collagen deposition was also measured using the image analysis system described above. Percent collagen volume for each region was calculated by adding the collagen areas and dividing that number by the sum of myocyte areas plus collagen areas, as previously described [24].

### Statistical analysis

Parameter reproducibility was analyzed twice by the same observer (intraobserver variability) and by 2 independent operators in 8 patients (interobserver variability); variability coefficients were 5.4% and 6.2%, respectively.

Qualitative variables were expressed as absolute values, proportions and/or percentages, with their 95% confidence intervals (CI). Continuous variables were expressed as means and standard deviations, after accepting their normal distribution with D'Agostino-Pearson's test; when variables were not distributed normally, they were expressed as medians and inter-quartile ranges. Comparison among discrete variables was performed with Pearson's  $\chi^2$  test, among continuous variables with the unpaired Student's t test for normal distributions and equal variances and for non-normal distributions with Mann-Whitney's U test. Association among continuous variables was determined with linear and nonlinear regression. To compare two or more independent groups, the one-way ANOVA test was used, with a *post-hoc* Tukey test to assess group differences. Tests were two-tailed and a p value < 0.05 was considered statistically significant.

## Results

The clinical characteristics of patients in the three groups (n = 26) are depicted in Table 1.

**Table 1.** Clinical, hemodynamic and echocardiographic variables in basal condition.

|  | Group 1           | Group 2a          | Group 2b          | P      |
|--|-------------------|-------------------|-------------------|--------|
| <b>Clinical variables</b>                                |                   |                   |                   |        |
| Age  | 68 ± 12           | 64.14 ± 9.92      | 71 ± 11.59        | NS     |
| Gender: male/female                                      | 2/5               | 3/4               | 9/3               |        |
| Systolic blood pressure [mm Hg]                          | 119.71 ± 22.84    | 125.14 ± 5.87     | 132 ± 9.03        | NS     |
| NYHA functional class for angina:                        |                   |                   |                   |        |
| II   | 3                 | 3                 | 1                 |        |
| III  | 1                 |                   | 2                 |        |
| IV   |                   | 1                 |                   |        |
| NYHA functional class for dyspnea:                       |                   |                   |                   |        |
| II   | 3                 | 6                 | 4                 |        |
| III  | 3                 |                   | 3                 |        |
| IV   |                   |                   |                   |        |
| Syncope  | 0                 | 1                 | 1                 | NS     |
| <b>Cardiac catheterization</b>                           |                   |                   |                   |        |
| LVESP [mm Hg]  | 202.5 ± 19.46     | 211.28 ± 40.47    | 193.16 ± 24.37    | NS     |
| +dP/dt <sub>max</sub> [mm Hg/s]                          | 2,230.75 ± 493.03 | 1,830.28 ± 346.98 | 2,231.55 ± 313.02 | 0.07   |
| tau <sub>50</sub>  | 24.99 ± 2.41      | 32.66 ± 5.96      | 32.52 ± 8.85      | NS     |
| <b>Echocardiography</b>                                  |                   |                   |                   |        |
| Ejection fraction [%]                                    | 75.71 ± 5.93      | 64 ± 6.03         | 66.72 ± 10.65     | 0.04   |
| End-systolic diameter [mm]                               | 29.74 ± 6.26      | 26.33 ± 5.39      | 33.37 ± 8.06      | NS     |
| End-diastolic diameter [mm]                              | 49.31 ± 5.29      | 48.16 ± 5.15      | 52.75 ± 4.15      | NS     |
| Myocardial mass index [g/m <sup>2</sup> ]                | 198 ± 85          | 162 ± 43          | 209 ± 42          | NS     |
| End-systolic meridional stress [kdynes/cm <sup>2</sup> ] | 42.54 ± 22.03     | 37.7 ± 14.98      | 51.67 ± 24.15     | NS     |
| Midwall fractional shortening [%]                        | 14.15 ± 3.95      | 14.96 ± 2.7       | 13.48 ± 4.35      | NS     |
| Midwall fractional shortening/stress                     | 18.68 ± 0.83      | 18.86 ± 0.56      | 18.05 ± 1.04      | NS     |
| Aortic valve area [cm <sup>2</sup> ]                     | 0.77 ± 0.26       | 0.45 ± 0.07       | 0.74 ± 0.15       | NS     |
| Mean aortic gradient [mm Hg]                             | 52.74 ± 18.87     | 66.83 ± 10.83     | 48.36 ± 9.42      | < 0.05 |
| Peak aortic gradient [mm Hg]                             | 89.28 ± 26.32     | 103.66 ± 15.06    | 80.09 ± 16.1      | 0.07   |

1 — compensated hypertrophy; 2a — decompensated hypertrophy without coronary artery disease; 2b — decompensated hypertrophy with coronary artery disease; LVESP — left ventricular end-systolic pressure; NS — not significant; NYHA — New York Heart Association;

### Cardiac structure and function

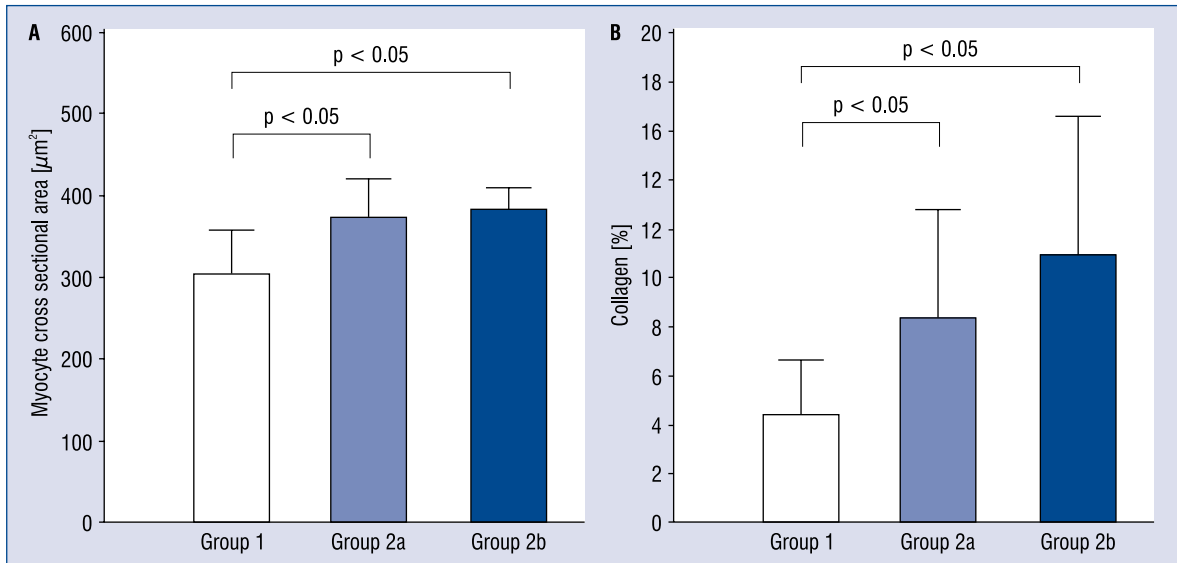
**Endomyocardial biopsy.** Differences among groups were seen in myocardial structure expressed by myocyte area ( $p < 0.01$ ) as well as by collagen volume ( $p < 0.01$ ) (Table 1). The LVMI was similar in all groups; however, morphometric analysis showed that in group 1 myocyte area and collagen volume were smaller than in groups with decompensated LVH (Figs. 1A, B).

Patients in G1 exhibited a proportional increase in collagen volume for a certain increase in myocyte area; such relation was lost in patients with decompensated LVH, in whom for a certain increase in myocyte area there was a dispropor-

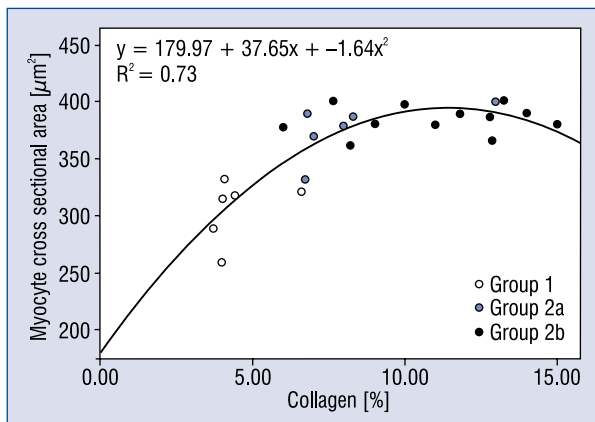
tionate rise in collagen volume; this phenomenon reached its maximum expression in patients with CAD (Fig. 2).

**Diastolic function.** In the absence of changes in diastolic diameters, the difference in LVEDP between the three groups attests to an increase in myocardial stiffness in the groups with decompensated LVH (Fig. 3).

All patients had impairment in myocardial relaxation, expressed by a change in tau and tau<sub>50</sub>, and without differences among groups (Table 1). The rise in LVEDP correlated directly with the changes in structure assessed by collagen volume (regression coefficient 0.97,  $p < 0.001$ ) (Fig. 4).



**Figure 1.** A. Differences in myocyte cross sectional area between groups; B. Differences in collagen volume expressed as percent between groups; \*p < 0.05 G1 vs. G2a and G2b.

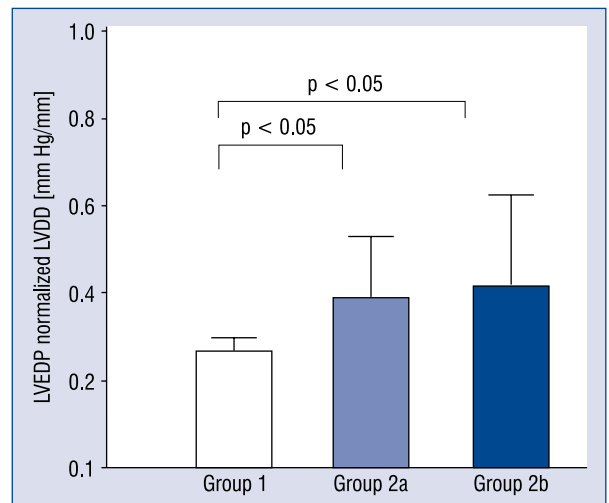


**Figure 2.** Quadratic function expressing the relation between collagen volume and the myocyte area in the various groups ( $R^2 = 0.73$ ).

A positive correlation,  $r = 0.53$ ,  $p = 0.04$ , was also seen between LVEDP and SGLS.

**Systolic function.** The LVEF was within normal limits in all patient groups, and there were no differences in LVMI, MFS at baseline and normalized by wall stress or LVESP measured by cardiac catheterization (Table 1). However, differences were seen in a preload-adjusted systolic function index ( $+dP/dt_{max}$  [mm Hg/s] normalized by LVEDP [mm Hg]) and in SGLS, thus, impairment of systolic function was more marked in patients with decompensated hypertrophy (Figs. 5, 6).

A positive correlation,  $r = 0.71$ ,  $p = 0.007$ , was found between the hemodynamic index of

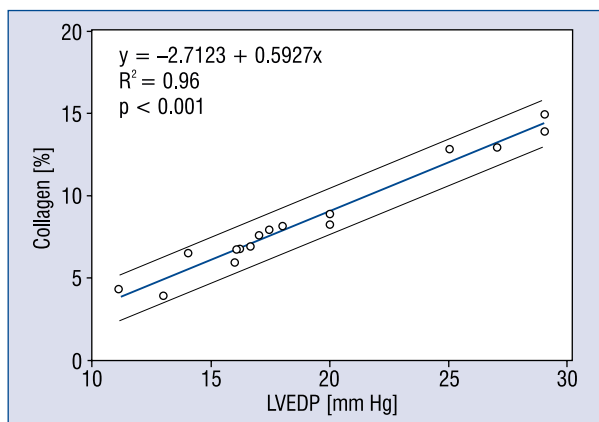


**Figure 3.** Graphic depicting differences in myocardial stiffness between groups; LVEDP — left ventricular end-diastolic pressure; LVDD — left ventricular diastolic diameter.

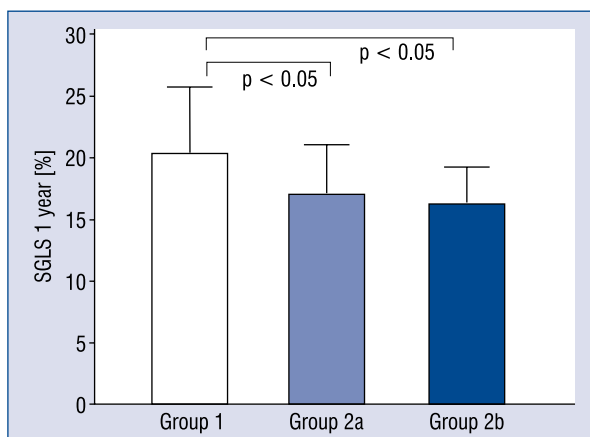
contractile status ( $+dP/dt_{max}$  [mm Hg/s] normalized by LVEDP [mm Hg]) and SGLS.

### Discussion

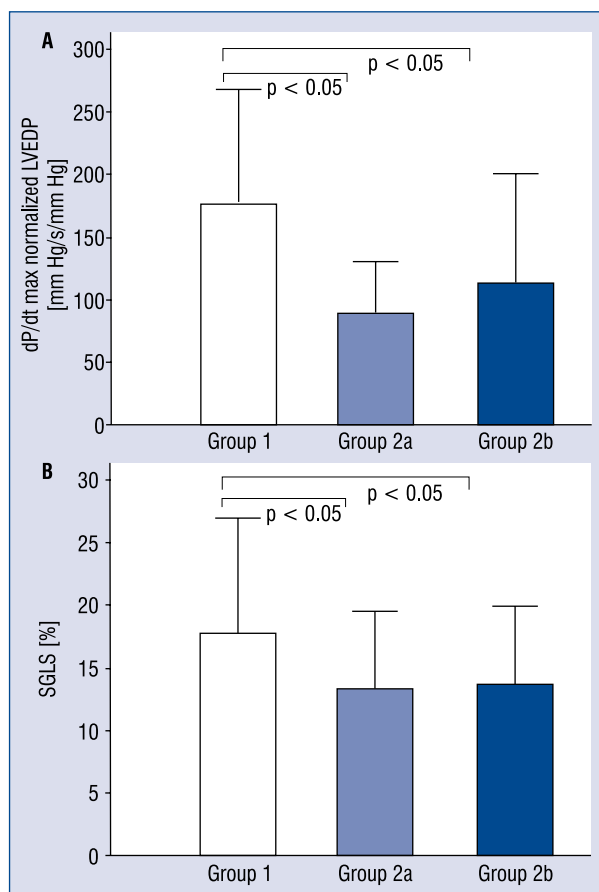
This study shows that in patients with severe AS and preserved LV function, the adaptive mechanism of hypertrophy exhibits various stages of progression, expressed by changes in LV function and structure, which allow to identify groups of patients with different degrees of myocardial



**Figure 4.** Linear regression of the relation between left ventricular end-diastolic pressure (LVEDP) in mm Hg and collagen volume in percent (correlation coefficient = 0.96,  $p < 0.001$ ).



**Figure 6.** Left ventricular peak systolic global longitudinal 2-dimensional strain (SGLS) at 1 year post aortic valve replacement, expressed as percent, for groups G1, G2a and G2b ( $*p < 0.05$  G1 vs. G2a and G2b).



**Figure 5. A.** Analysis of  $+dP/dt_{max}$  (mm Hg/s) normalized by left ventricular end-diastolic pressure (LVEDP), for the three groups. ( $*p < 0.05$  G1 vs. G2a and G2b); **B.** Left ventricular peak systolic global longitudinal 2-dimensional strain (SGLS), expressed as percent, for the three groups ( $*p < 0.05$  G1 vs. G2a and G2b).

impairment. Early identification of such a myocardial impairment is important for decision making in valve disease in general, and particularly in AS. In the cases of increased wall stress, the myocardium develops ventricular hypertrophy as a compensatory response; such hypertrophy presents as quantitative and qualitative changes, increase in mass and changes in structure. In the present study, we considered the increase in collagen volume a qualitative change which occurred without differences in LVMI between groups. As Weber [25] stated: “It is not the quantity but rather the quality of myocardium that distinguishes hypertensive heart disease from adaptive hypertrophy of the athlete”.

Decompensated groups exhibit greater impairment in structure characterized by a larger myocyte area and greater increase in collagen, with marked increase in myocardial stiffness. This impairment in diastolic function and its correlation with changes in structure was described in previous studies [10, 11], albeit in patients with less preserved EF than patients in our population, and without changes that allow to discriminate different groups with different stages of disease progression.

Although the increase in collagen volume of the compensated group is twofold the reference values for a normal population [26], it is much less than that found in the decompensated group. Increase in collagen is probably due to impairment in myocardial perfusion, secondary to the loss of coronary vasodilatory reserve and elevated wall stress, resulting in a predominant increase in subendocardial fibrosis as the disease progresses

**Table 2.** One-year echocardiography data.

| Echocardiography at 1 year                | Group 1       | Group 2a       | Group 2b       | P    |
|---|---------------|----------------|----------------|------|
| Ejection fraction [%]                     | 62.75 ± 13.81 | 55             | 65 ± 5.83      | NS   |
| End-systolic diameter [mm]                | 27.5 ± 2.38   | 37             | 30.75 ± 4.27   | NS   |
| End-diastolic diameter [mm]               | 48.25 ± 2.87  | 61             | 48.75 ± 3.77   | NS   |
| Myocardial mass index [g/m <sup>2</sup> ] | 136.2 ± 54.97 | 158.66 ± 24.36 | 159.18 ± 35.45 | NS   |
| Midwall fractional shortening [%]         | 17.63 ± 1.42  | 16.24 ± 2.51   | 14.62 ± 1.35   | 0.01 |
| Midwall fractional shortening/stress      | 18.09 ± 0.49  | 18.29 ± 0.22   | 18.47 ± 0.58   | NS   |

1 — compensated hypertrophy; 2a — decompensated hypertrophy without coronary artery disease; 2b — decompensated hypertrophy with coronary artery disease; NS — not significant

[27, 28]. A special condition is that of patients with concomitant CAD, in whom this mechanism adds on to those previously described.

All groups had impaired myocardial relaxation, as assessed by  $\tau_{50}$ ; these changes seen in AS have been previously described in animal models [29], as well as in clinical studies [30], and are related (among other processes) to intracellular movement of calcium, thus it could be part of the mechanisms resulting in progressive failure of the hypertrophic myocardium [31].

Impairment of diastolic function in AS has been described as a prognostic factor, pre- and postoperatively, and some authors have suggested that its finding should be considered for early surgical intervention [32].

All patients in our study had a normal EF, a parameter that is used to express absence of failure of the global LV function; however, this index is subject to variations depending on the chamber's geometry, afterload and increase in mass [33–35], among other variables. Hence, EF is more precise to evaluate pump function than ventricular function, since it mainly expresses the radial function of the myocardium and is less affected by abnormalities of the subendocardium [36]. A more specific index of the assessment of function in the presence of hypertrophy, MFS [37], was normal in all group after normalizing by wall stress, probably because it was evaluated in patients with normal EF and an end-systolic stress which did not exceed 120 kdynes/cm<sup>2</sup> (according to several studies, LVH should be considered inappropriate when values exceed this cutoff level) [18]; this could explain the failure of this index in detecting contractile function impairment in this study.

More sensitive parameters useful to assess contractile status are:  $+dP/dt_{\max}$  [38] normalized by LVEDP, and SGLS, which allows to assess

contractile properties of the myocardium [39] in various scenarios including AS [13], confirmed the impairment of systolic function, especially in decompensated groups, and could thus be useful tools to characterize subtle changes in ventricular function. Interestingly, a significant positive correlation was observed between both parameters assessing LV contractile status.

This myocardial impairment and structural changes initially and mainly involve the subendocardium [40], affecting longitudinal function, which is not well assessed by EF, but can be assessed by other indices that use M-mode and/or tissue Doppler imaging to analyze the lateral displacement of the mitral annulus [41].

Various authors have observed the association between strain impairment in patients with SSAS and its impact on increased risk and clinical events in the long-term follow-up [42].

Lancellotti et al. [43] studied patients with asymptomatic AS and saw that a SGLS < 15.9% was a prognostic marker of an adverse course. In our patients, the compensated group exhibited values above the cutoff point, whereas in the decompensated group with and without CAD, values were 13.5% and 13.6%, respectively. Other authors demonstrated that SGLS returned to normal values at 1 year post valve replacement [44]; in our study SGLS values returned to normal only in the compensated group (Table 2).

Correlation between the degree of fibrosis and changes in strain has been described by other authors [45] and by our group [14], as well as the improvement and/or normalization of strain values after aortic valve replacement [46]; however, we are not aware of any publication showing that in patients with preserved EF and MFS at baseline, two groups of patients could be distinguished by structure, function, baseline systo-diastolic function and a different strain pattern at 1 year. Evi-

dence shows that changes in structure, particularly fibrosis, are an early finding in the progression of AS [47] and determine aspects of systolic, as well as diastolic function [48], which entail prognostic value and affect long-term survival following aortic valve replacement [49]. This adverse progression is related to myocardial failure which is probably an evolving process, as described by Meerson [50], and of which many aspects remain unknown. Early detection of myocardial impairment is clinically important, and detecting the various stages of progression of hypertrophy can be very useful for decision making.

The present study contributes information about the changes in cardiac structure and function in AS that may be useful for clinical management, and suggest a transition in the progression of ventricular hypertrophy to myocardial failure. Some of these changes remain abnormal at 1 year after valve replacement in the group of patients with decompensated hypertrophy.

### Limitations of the study

Our results should be validated in a larger number of patients. The information found is only applicable to a symptomatic patient population. One-year follow-up does not provide information about the clinical course and LV function changes in the mid- and long-term follow-up.

### Conclusions

Patients with SSAS and preserved EF who progress to decompensated LVH characterized by an increase in LVEDP, exhibit impairment in their myocardial structure and diastolic function expressed by changes in ventricular relaxation and myocardial stiffness, as well as in their systolic function expressed by hemodynamic and myocardial strain indices.

**Conflict of interest:** None declared

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