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Afterload it's importance in surgical decision making in severe aortic stenosis

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Abstract

The present study investigates the role of hemodynamic afterload in severe aortic stenosis and its influence on ventricular function. In this disease, heart failure due to intrinsic myocardial damage causes high surgical mortality. When the patient survives the surgical time; functional class deteriorates frequently in medium-term and mortality is also high. On the other hand, when heart failure is due to excessive afterload and normal myocardial structure, reducing excessive afterload is supposed to normalize ventricular function, reduce surgical mortality, and improve long-term survival. In this prospective study we tried to demonstrate the value of ventricular afterload on surgical prognosis in tight aortic valve stenosis in immediate and medium-term..

Introduction

Regarding the treatment of severe aortic stenosis (SAS), the indication of the optimal time for the intervention is based on several issues: severity of the valve disease, symptoms, function of the heart primary assessed by the left ventricular ejection fraction (LVEF), age of patients, co-morbidities, stress test, degree of aortic valve calcification and patient's life expectancy [1].

Surgical results in terms of mortality, functional class and expectancy of life can be considered as very satisfactory in general1 and in asymptomatic patients [2-5]. However, the criteria to indicate surgery in asymptomatic patients and in those with heart failure with low LVEF are subjective and not quantifiable [1]. Regarding the asymptomatic patients with LVEF> 50%, it has been reported that many of them have reserved prognosis, given that up to 60% will develop symptoms and about 75% will die or require aortic valve replacement [3]. The (LVEF) has been used as a standard way to assess the surgical risk and postoperative results [6,7]. However, the LVEF accurately assesses the function of the left ventricle, but not the intrinsic components that affect it [8]. In fact, ventricular function has two essential components: the contractility, and the instantaneous hemodynamic loads with which the heart operates.

From the end of the 19th century, RH Woods et al., showed that Laplace's Law was applicable in the human heart to know the tension to which these tissues are exposed during different moments of cardiac function [9]. This issue was later studied by Sandler and Dodge in the human heart, who did cardiac catheterization and angiographic studies to describe the concepts of tension and stress [10]. Gunther and Grossman demonstrated in patients with aortic stenosis that there is an inverse relationship between SWS (estimated on Laplace's Law) and LVEF; this means that SWS in fact matches to left ventricular afterload [11]. Subsequently, WP Hood et al., demonstrated that when the systolic pressure is increased, the hypercontractility produced by myocardial hypertrophy normalizes the systolic stress in the left ventricle [12]. With these findings, Carabello et al., studied [13] patients with severe aortic stenosis (SAS) and a LVEF less than 50% and found that in patients with a severely reduced LVEF but with high SWS, there was no surgical mortality when they were taken to aortic valve replacement; furthermore, LVEF was normalized; conversely, all patients with a severely reduced LVEF and a low or pseudonormalized afterload (SWS) died in the postoperative period [13].

All these findings are consistent that when a reduced LVEF is due to excessive afterload, the aortic valve replacement relieves this afterload, and because there is no intrinsic myocardial damage, the heart recovers its function and a good prognosis can be expected. This issue was studied extensively by John Ross Jr. and was called the "afterload mismatch" [14].

Currently, the assessment of the surgical indication of patients with aortic stenosis does not include the evaluation of the afterload to which the left ventricle is exposed, neither in patients with

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normal LVEF, nor in patients with a reduced LVEF (heart failure).

Recently, left ventricular afterload was accurately calculated by 2D echocardiography and by nuclear magnetic resonance [15-17].

In this work, we specifically aimed to assess left ventricular afterload [16] (SWS) and specially the relationship with myocardial hypertrophy [18], in an attempt to complement the study of ventricular function and look for quantifiable parameters that allow us to approach the optimal time to indication the surgical intervention in patients with SAS.

Methods

A cohort study was performed in patients with severe aortic stenosis. The time zero of the cohort was at the time of diagnosis. All patients who presented to the Department of Ecocardiography of our tertiary care center with diagnosis of severe aortic stenosis were evaluated for eligibility. The cohort was followed since January 2015 to October 2017.

Participants

We included patients over 18 years of age, of any gender, with complete clinical information in the electronic records, and with complete echocardiographic studies of adequate quality to perform the measurements. We excluded patients with poor echocardiographic window, tangential views. Patients with ischemic heart disease, wall anomalies related to a coronary territory found on the echocardiography examination, aortic or mitral regurgitation greater than or equal to moderate degree, and diagnosis of atrial fibrillation were excluded as well.

Variables

The main outcome of our study was mortality from any cause evaluated as time to event. Our main predictor was SWS. Clinical and echocardiographic variables related to the severity of aortic stenosis were recorded.

Diagnostic criteria

The definition of SAS recommended by the American Association of Echocardiography was adopted for this study: [21] aortic valve area less than 1.0 cm2 with a mean gradient greater than 40 mmHg. The calculation of the valve area was made using the continuity equation [22] and the mean gradient was determined by the continuous Doppler spectrum.

Data source / measures

The follow-up of the patients was carried out through electronic records of the hospital. According to the Institute's policies, all patients are followed up every 4 to 6 months, so it was feasible to obtain a reliable and complete follow-up in all patients.

For the echocardiographic study, clinical characteristics of the patients were recorded: gender, age, weight, height, and body surface area were quantified. All patients underwent 2D echocardiography, pulsed Doppler, continuous Doppler and color coded according to the recommendations of international guidelines19. All echocardiographic measurements were performed off-line using the Syngo Dynamics software from Siemens.

With the patient at rest, the heart rate and blood pressure were quantified using a mercurial sphygmomanometer. After that, the echo 2D study was performed with the patient in the left lateral decubitus position. The long axis of the left ventricle was achieved using the parasternal approach. In diastole, the thickness of the interventricular septum (IVS), the diastolic diameter (DD) and the posterior wall (PW) of the LV were measured, taking special care that the cut where perpendicular to the greater axis of the left ventricle. In systole, when the closest approach of SIV and PP was achieved, the systolic diameter (SD) was measured.

With the equation: DD - SD / DD the shortening fraction was obtained (SF).

With this same view, the diameter of the aortic root (AOR) was measured at the end of diastole and at the end of systole, the diameter of the left atrium (LA) was also measured, both following the guidelines of the left atrium. American Society of Echocardiography [19].

The parasternal long axis of the left ventricle was used in systole, to measure the diameter of the aortic valve annulus, and its area was calculated (π x r^2). With the so called "5-chamber apical view", the flow was measured using pulsed Doppler at the level of the left ventricular outflow tract below the aortic valve and the velocity / time integral (VTI) was calculated. Likewise, continuous Doppler was used to measure the maximum flow velocity in the aortic root and thus to measure the maximum trans-aortic gradient; the ITV was obtained to measure the average gradient using the apical or right parasternal view at the level of the 2nd right intercostal space. The aortic valve area was calculated by means of the continuity equation20. The maximum gradient was also measured to obtain the maximum intraventricular systolic pressure by adding it to the systolic blood pressure obtained with the sphygmomanometer.

Using the 4-chamber apical view, the endocardium of the left ventricle was drawn in diastole and in systole to quantify the ejection fraction (FE). We used a monoplanar method and the left ventricular mass was also calculated according to the recommendations of the American Society of Echocardiography [19].

Special measures of ventricular function

Since 1976 Lincoln E. Ford, described that the relationship between the thickness of the wall and the radius of the cavity under normal conditions remains stable regardless the size of the heart, demonstrating that the mass / volume ratio and its derivative thickness/radius (h/r) in diastole, are constants that govern cardiac physiology [21]. Based on these principles and using the technique described by Stack RS et al. [22], at Duke University, left ventricular thickness/radius in diastole was quantified (Figure 1). We used the following definitions:

Using a short parasternal axis in diastole, at the level of the papillary muscles, the epicardial area (A1) and the endocardial area (A2) were measured, r1-r2 = thickness = h, then: h/r2 = relationship h/r were calculated. (Figure 1), for study of preload (relationship thickness/radius) (LaPlace Law) [24].

Definition of afterload

"It is the resistance that the myocardim has to overcome in order to raise intraventricular pressure, open the aortic valve and expel its content into the great vessels", it is calculated using LaPlace Law [10,11,12,16,24].

Calculation

In the same axis in systole the epicardial area (A3), minus the endocardial area (A4), let us to estimate the thickness of the left ventricular wall, an essential parameter for the calculation of SWS (afterload) (Figure 2).

Wall stress. It is the force that tends to separate the myofibrils from each other by squared centimeter [11].

Systolic wall stress (SWS): It is the force per unit of sectoral area,

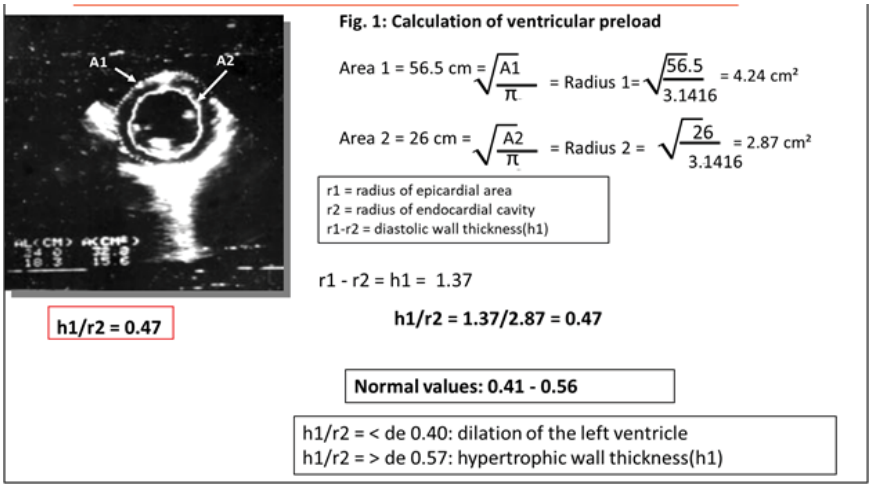

Figure 1. *Calculation - the relationship h1/r2 Preload*

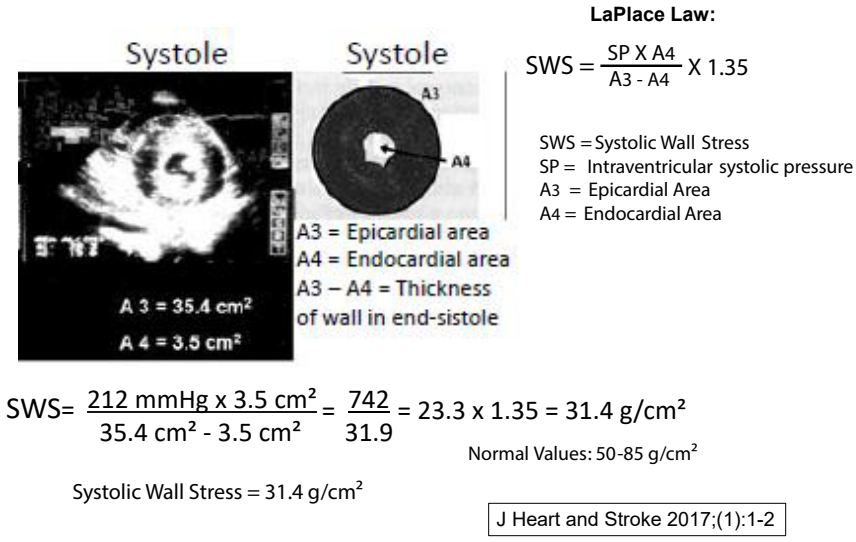

Figure 2. *Afterload calculation*

which opposes to ventricular contraction to achieve blood ejection to the great vessels [11,16].

1. by the formula described in figure 1. Wall thickness is: R1 – R2 = h1 and h1/r2 = Thickness/radius ratio for calculate left ventricular hypertrophy and preload [22].

Calculation of SWS by echocardiography according to the Laplace Law [15,16,18,24] (Figure 2).

$S = [(P \times r)/h] \times 1.35$

Where P is equivalent to the intraventricular systolic pressure that in aortic stenosis is calculated by adding the maximum systolic gradient obtained by continuous Doppler to the aortic systolic pressure obtained by the sphygmomanometer [13]. r corresponds to area 4 (systolic area of the ventricular cavity) (figures 1B and 2) and h corresponds to the systolic thickness of the left ventricle: area 3 - area 4 (Figure 2). When the equation is finished, the result is multiplied by 1.35 which is the correction factor to transform mmHg into grams per squared centimeter [13]. (Figure 2) shows the calculation of SWS in a patient with SAS. Note that even when intraventricular systolic pressure is very high, hypertrophy normalizes afterload by achieving greater contractile force (Figure 2)

Bias

To avoid potential sources of bias, all patients who met the eligibility criteria were included. Researchers who performed the echocardiographic measurements were unaware of the evolution of the patients and whether or not they presented the event.

Statistical analysis

An exploratory analysis was carried and missing values were identified, which were retrieved from the electronic file. The descriptive analysis for the quantitative variables with normal distribution was performed with mean and standard deviation and for variables with a non-parametric distribution with median and interquartile range. The qualitative variables were described with absolute and relative frequencies. For the quantitative variables with normal distribution, means were compared with the Student's T test for independent groups. For those with non-normal distribution, medians were compared with the Mann-Whitney U test. The nominal variables were compared with $\chi 2$ or Fisher's exact test in case of expected frequencies ≤5. The receiver operating characteristic (ROC) curve was used to identify different cut-off values of SWS to

predict mortality. For the main outcome, bivariate and multivariate logistic regression was performed to determine the association of each covariate with the outcome. Patients were divided in three different groups according to LVEF and SWS. Survival curves were assessed with the Kaplan-Meier method and compared with the log Rank test. In all cases, a value of p <0.05 was considered statistically significant.

Results

Participants

From 2015 to 2017, 420 patients diagnosed with SAS were evaluated for eligibility. We excluded 313 patients due to inadequate echocardiographic study or other valve diseases. We included 107 patients with SAS in the final analysis. Mean age was 64±12 years, male 63%. Mean LVEF was 53±23%, and mean gradient was 53±22 mmHg.

Echocardiography

Patients were divided into 2 groups according to the LVEF: the first group included patients with a LVEF ≥ 50% (57 patients) and the second group were patients with a LVEF <50% (50 patients). Systolic blood pressure, diastolic blood pressure and intraventricular pressure were significantly higher in the normal LVEF group compared to the low LVEF group. The diameter and volume of the left atrium, the diastolic diameter of the LV and the end-systolic diameter of the LV, were significantly higher in the group of low LVEF. The h/r ratio was lower in the group with low LVEF. SWS was greater in patients with low LVEF (Table 1).

The association between LVEF and SWS was evaluated with a scatter plot. A negative correlation was observed with a Pearson correlation coefficient of -0.68, p<0.001 (Figure 3).

Mortality

During the follow-up of the cohort, 58% of the patients underwent aortic valve replacement. Mortality was 11% during a median follow-up of 326 days.

With respect to the main objective of our study, the effect of afterload on surgical indication and its postoperative evolution at the medium term, the bivariate analysis showed that only the left atrium volume and the LVEF showed a trend towards statistical significance. At multivariate analysis, these variables were included in addition to the SWS given that it was the main objective of this study. As shown in table 2, after stepwise backward-elimination, only the LVEF and SWS were independent predictors of mortality.

In the subgroup of patients with low LVEF, we performed a ROC

Table 1. *Baseline characteristics of the study's patients*

	LVEF ≥50% (n=57)	**LVEF <50% (n=50)**	**p**
Age (years)	66±11	62±12	0.077
BSA (m2)	1.72±0.16	1.75±0.20	0.325
Male	34 (60%)	33 (66%)	0.498
Systolic blood pressure (mmHg)	126±19	111±16	<0.001
Diastolic blood pressure (mmHg)	74±12	68±11	0.013
Left atrial diameter (mm)	37±6	44±7	<0.001
Left atrial volume (ml/m^2)	37±12	54±22	<0.001
LVEDD (mm)	41±7	52±7	<0.001
LVESD (mm)	25±8	44±8	<0.001
Fractional shortening (%)	40±12	15±7	<0.001
Septum wall dimension (mm)	15±4	13±3	0.009
Posterior wall dimension (mm)	13±4	12±3	0.740
h1/r2	0.77±0.23	0.53±0.14	<0.001
Systolic wall stress (g/cm^2)	37.7±25.8	102.6±51.0	<0.001
Mass (g/m^2)	128±41	160±55	0.001
Peak aortic velocity (m/s)	4.6±0.75	4.3±0.15	0.046
Maximum aortic gradient (mmHg)	89±30	79±37	0.128
Mean aortic gradient (mmHg)	54±18	50±25	0.272
Aortic valve area (cm^2)	0.54±0.22	0.43±0.19	0.007
Intra-ventricular pressure (mmHg)	213±36	189±36	<0.001
Information is shown as the mean ± standard deviation or n (%).			
LVEDD: left ventricular end-diastolic dimension. LVEF: left ventricular ejection fraction. LVESD: left ventricular end-systolic dimension.			

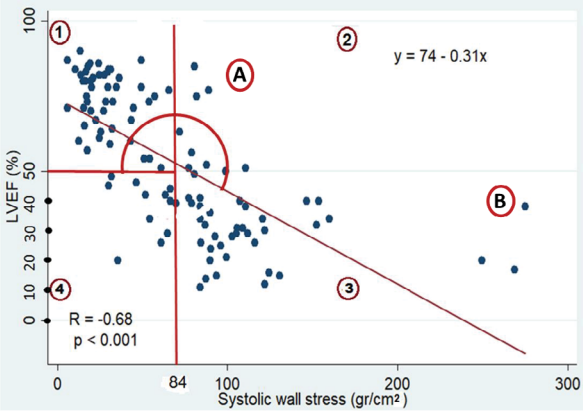

Figure 3. *Correlation between LVEF (%) and systolic wall stress (g/cm²)*

Table 2*. Bivariate and multivariate analysis for the prediction of mortality.*

	Bivariate		Multivariate*	
	OR (95% CI)	p	OR (95% CI)	p
Age (years)	0.97 (0.92 – 1.03)	0.415	--	--
Male	1.01 (0.28 – 3.70)	0.990	--	--
Left atrial diameter (mm)	1.07 (0.98 – 1.16)	0.106	--	--
Left atrial volume (ml/m²)	1.03 (0.99 – 1.05)	0.062	--	--
LVEDD (mm)	1.02 (0.95 – 1.09)	0.571	--	--
LVESD (mm)	1.01 (0.96 – 1.06)	0.594	--	--
Fractional shortening (%)	0.98 (0.96 – 1.02)	0.472	--	--
h1/r²	1.20 (0.08 – 17.8)	0.893	--	--
LVEF (%)	0.97 (0.94 – 1.00)	0.069	0.93 (0.89 – 0.98)	0.006
Systolic wall stress (g/cm²)	0.99 (0.98 – 1.01)	0.709	0.97 (0.94 – 0.99)	0.039
Mass (g/m²)	1.00 (0.99 – 1.01)	0.819	--	--
Peak aortic velocity (m/s)	1.20 (0.62 – 2.35)	0.577	--	--
Mean aortic gradient (mmHg)	1.00 (0.98 – 1.03)	0.606	--	--
Aortic valve area (cm²)	0.54 (0.01 – 1.92)	0.110	--	--
Intra-ventricular pressure (mmHg)	0.99 (0.98 – 1.01)	0.500	--	--

* The full model included the following variables: left atrial volume, LVEF, systolic wall stress and aortic valve area. Only variables with a p<0.05 were retained in the final model after stepwise backward elimination.
LVEDD: left ventricular end-diastolic dimension. LVEF: left ventricular ejection fraction. LVESD: left ventricular end-systolic dimension.

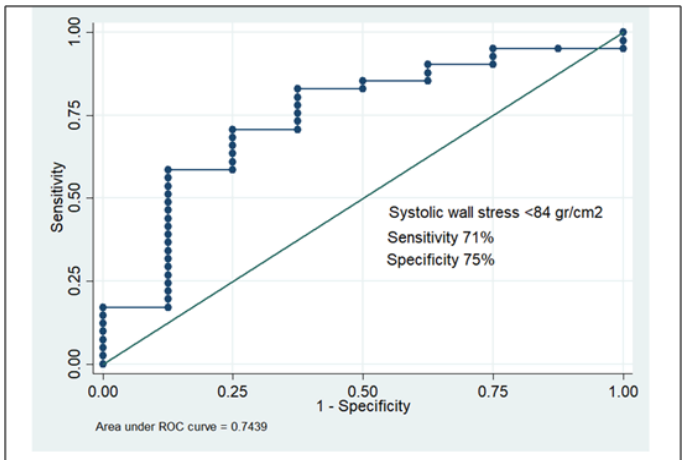

Figure 4. *Correlation between LVEF (%) and systolic wall stress (g/cm²)*

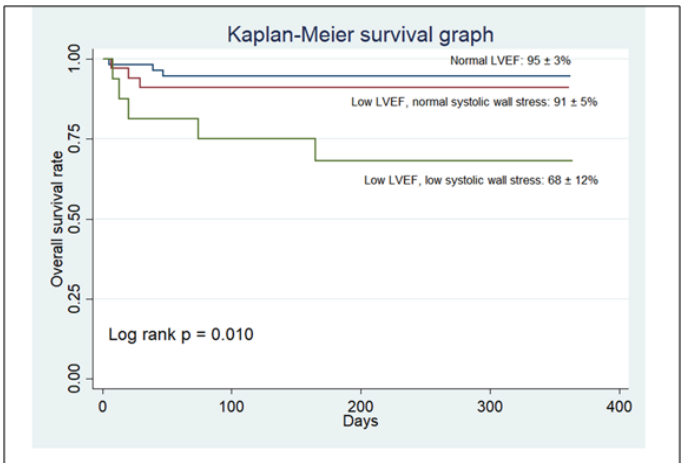

Figure 5. *Survival analysis with the Kalpan-Meier method in patients with normal LVEF, low LVEF and normal or low systolic wall stress*

curve to determine the optimal cut-off point at which the SWS predicted mortality. We observed that the best cut point was 84 g/cm^2, with a sensitivity and specificity of 71% and 75%, respectively. (Figure 4).

For the survival analysis, this cut-off point was used to stratify the patients into three groups. The group 1 included patients with normal LVEF (≥50%) and any level of SWS. The group 2 included patients with low LVEF (<50%) but a SWS ≥84 g/cm2. Finally, the group 3 included patients with low LVEF and a SWS <84-100 g/cm^2 or pseudonormalized. The Kaplan-Meier method showed that at a median follow-up of 326 days, patients in group 1 and 2 had a significantly better survival compared to patients in group 3 (95±3%, vs. 91±5%, vs. 68±12%, respectively; p=0.010). (Figure 5).

Sensitivity analysis

Because the aortic valve replacement represents a confounding variable, a sensitivity analysis was performed. The multivariate analysis was repeated including LVEF, SWS, and "surgery" as a covariates. The multivariate analysis showed that both LVEF (OR 0.93, 95% CI 0.89-0.97, p=0.006) and SWS (OR 0.97, 95% CI 0.94-0.99, p=0.038) remained independent predictors of mortality even after adjusting for surgery.

Myocardial hypertrophy in aortic stenosis

In this project, we studied left ventricular hypertrophy, based on the fundamental concepts previously described by Sasayama [18], Gaasch [25], Grossman [26], and Weber [27]. Using the technique of Stack R et al. [22]. It was possible accurately quantify the LVH and know its behavior in different conditions that affect cardiac function in aortic stenosis.

Role of afterload in patients with aortic stenosis

In aortic stenosis, it is essential to know along with LVH, the role of the afterload (SWS) [11-15]. In fact, in patients with aortic stenosis and adequate ventricular hypertrophy, we found that afterload is at normal or even reduced levels, which is consistent with previous reports [12,13]. In these cases, hypertrophy works as an efficient mechanism and maintains the patient with normal ventricular function and in functional class I, without higher metabolic cost (MVO2) [28,29]. However, if the afterload continues to increase, the ventriculary hypertrophy stops being an adaptive mechanism. In this study, we found that when it increases beyond 84g/cm^2, the left ventricle begins its dilation using the Starling mechanism, but later the LVEF may reduce and heart failure appears. Nevertheless, in these cases the low LVEF is due to excessive afterload, and surgical treatment is indicated, even in patients with severe heart failure (low LVEF), because by installing an aortic prosthesis and reducing afterload, ventricular function is normalized, and thus it confers a low risk surgical because the contractile performance is conserved (there is no myocardial damage) [14-30]. In these cases, one might expect a significant increase in survival, changing the natural history of the disease as we found in this study. Conversely, if the patient has a low LVEF and low afterload (SWS <84 g / cm^2), mortality is expected to very high, because the low LVEF is due to the presence of intrinsic myocardial damage [13-15] and pathological hypertrophy [26]. This is the reason for the high mortality at short-term mortality found it the mentioned patients.

Role of left ventricular hypertrophy, LVEF and afterload in the surgical indication of aortic stenosis

We accurately quantified the left ventricular hypertrophy and the effect it exerts in patients with aortic stenosis and normal or low LVEF (Figure 2). The ventricular hypertrophy acts as an adaptive process [26] that increases contraction strength [8] and systolic thickness of the ventricular wall. We found that the h1/r2 ratio in diastole (Figure 2A) and the wall thickness in systole are significantly increased (Figure 2B) and this allows to normalize afterload (SWS).

In this work, we showed that patients with SAS, low LVEF and SWS <84 gr/cm^2 have significantly higher mortality compared to patients with normal LVEF or SWS > 84 gr/cm^2. Therefore, we conclude that on patients with severe aortic stenosis and a low LVEF (<50%), the ideal time to surgically intervene these subjects is when the afterload is high (SWS ≥84 gr/cm^2), because these patients receive greater benefit with the surgical treatment that is evident by the clear reduction in mortality [30]. As above mentioned, this happens because the low LVEF is caused by a very high afterload because in these cases there is no intrinsic contractile damage (Afterload mistmach) [14,30].

On the other hand, if the patient has a low LVEF and the SWS is "normal" or pseudo-normalized (<84 g/cm^2), the surgical risk will be very high. Even if the patient survives the surgery, high mortality might be expected given that these cases reflect intrinsic myocardial damage, due to pathological hypertrophy that is not alleviated by the reduction of afterload when installing an aortic prosthesis [14,15,26].

Limitations

The main limitation of our study is its observational nature and that it was carried out in a single center. The fact that not all patients have received surgical treatment could be considered as a limitation; however, in the sensitivity analysis we demonstrated that the association of low afterload and low LVEF with higher mortality is maintained in patients with and without surgical treatment. Confirmation of these results in other centers is warranted.

Conclusions

Although it is true that LVEF is a key predictor of surgical mortality, currently, the assessment of the surgical indication in patients with (SAS), does not include the evaluation of the afterload to which the left ventricle is exposed, neither in patients with normal or reduced LVEF; specially in patients with a heart failure; if the intrinsic myocardial damage is responsible for heart failure, it is to be expected that postoperative high mortality or poor course and short or intermediate term; if on the contrary LVEF is due to an excessive afterload; surgical correct the excessive afterload.

We expected low operative mortality, good results and long survival In this work, we aimed to assess left ventricular afterload (SWS) and myocardial hypertrophy [11,18] by noninvasive technics an attempt to complement the study of ventricular function and look for quantifiable parameters that allow us to approach the optimal time to indicate the surgical intervention of patients with SAS, especially in patients with severe heart failure.

The results obtained in this investigation provide support to include the quantitative study of left ventricular hypertrophy as well as the quantification of afterload (both non-invasive methods), to assess the surgical indication of aortic stenosis with greater precision, specifically in asymptomatic patients and in those with reduced LVEF. Finally, when the indication is accurate, not only surgical success is obtained,

In patients with aortic stenosis with great hemodynamic overload, the calculation of afterload is essential to make an appropriate assessment, which is not only a rational guide for surgical indication, but it will also be an aid that can reduce operative morality and improve patient survival. long-term [15,16,30].

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