Impact of Hypertension on Ventricular Remodeling in Patients with Aortic Stenosis

João Carlos Hueb, João T. R. Vicentini, Meliza Goi Roscani, Daniéliso Fusco, Ricardo Mattos Ferreira, Silméia García Zanatti, Katashi Okoshi, Beatriz B. Matsubara

Hospital das Clínicas da Faculdade de Medicina de Botucatu - Unesp, Botucatu, SP - Brazil

Abstract

Background: Left ventricular hypertrophy (LVH) is a marker of increased cardiovascular risk and is frequently associated with both arterial hypertension (AH) and aortic stenosis (AoS). Also, these two maladies may co-exit in a same patient. However, in these cases, it is not clear the impact of each one in LVH.

Objective: To evaluate LVH and ventricular geometry in patients with AS associated or not with arterial hypertension.

Methods: This was a retrospective, observational and transversal study, including 298 consecutive patients with echocardiographic diagnosis of AoS. LVH was defined as myocardial mass > 224g for men and > 162g for women. Patients were classified as having mild (peak gradient < 30 mmHg), moderate (between 30 and 50 mmHg) or severe (> 50 mmHg) AoS and separated into two subgroups: with and without hypertension.

Results: AH was associated with increased ventricular mass in all three levels of aortic stenosis (mild AS: 172 ± 45g vs 223 ± 73g, p < 0.0001 moderate AoS: 189 ± 77 g vs 245 ± 81g, p = 0.0313 severe AoS: 200 ± 62g vs 252 ± 88g, p = 0.0372), and increased risk of LVH (OR = 2.1 CI95%:1.2-3.6 p = 0.012). Regarding to geometric remodeling, hypertensive patients with severe AS presented a significant increase in frequency of concentric hypertrophy, when compared with those without hypertension (p = 0.013).

Conclusion: Hypertension is an additional factor of increased left ventricular mass in patients with AS. Also, hypertension was influential in ventricular geometry. (Arq Bras Cardiol 2011; 97(3) : 254-259)

Keywords: Aortic valve stenosis; hypertrophy, left ventricular; hypertension; heart failure.

Introduction

Remodeling and hypertrophy of the left ventricle (LV) are adaptive responses to chronic systolic pressure overload commonly found in patients with hypertension (H) and aortic valve stenosis (AoS). On the other hand, hypertrophy is the starting point for myocardial dysfunction whose end result is heart failure, in addition, as a target organ damage, it is associated with higher cardiovascular risk. Also, not very rarely, we find association of these diseases, i.e., hypertension in patients with aortic valve stenosis.

Echocardiography is a very accurate and sensitive tool to detect and quantify left ventricular hypertrophy. Besides, through this method, it is possible to set the existing remodeling standard, whose importance relates to the fact that cardiovascular risk varies with ventricular geometry, mostly in cases of concentric hypertrophy, followed by eccentric hypertrophy and concentric remodeling. Thus, despite the relevance of this issue, few studies have assessed the impact of hypertension on the risk of LVH in patients with AoS.

The aim of this study was to evaluate the influence of hypertension on the degree of hypertrophy and pattern of ventricular geometry in patients with AoS.

Methods

Patients

This study was approved by the local Research Ethics Committee (OF.496/2007-CEP). It is a retrospective, observational and cross-sectional study including 298 consecutive patients. In our institution, all patients underwent echocardiographic examinations from January 2006 to June 2007, which showed aortic valve stenosis of any degree, irrespective of symptoms. For patients followed up, requests for tests were issued in specialty clinics or at the hospital admission units or emergency rooms.

Exclusion criteria

- Tests with technical quality that could interfere with the analysis of structural and functional cardiac abnormalities.
- Age over 18 years.
• Previous surgical repair.
• History of dilated cardiomyopathy unrelated to aortic valve lesions.
• Other valve lesions of greater than mild degree.

Data acquisition
From the echocardiographic reports available on the computer network of Hospital das Clínicas and in the medical records the following data were obtained: age, gender and prior diagnosis of hypertension, and the following echocardiographic parameters: left ventricular mass (VM), relative wall thickness (RWT) and peak aortic pressure gradient.

Echocardiography
A complete echocardiographic study was performed in all patients considered. In these examinations, we used the following ultrasound equipment: Philips HDI 5000, Toshiba Power Vision and Hewlett-Packard Sonus 2000 with phased-array transducers with frequencies ranging from 2.5 to 3.5 MHz. In the echocardiographic study, we considered the standards and techniques recommended by the American Society of Echocardiography. The LV myocardial mass (FM) was determined by the formula Devereux3 from the left ventricle diastolic diameter (DD), posterior wall thickness (PWT) and interventricular septum (IVS), measured during diastole (MV (g) = 0.8 \times (DD + IVS + PW)^{1.26} + 0.6), considering as normal values ≤ 224 g in men and ≤ 162 g in women. The relative wall thickness was calculated using the formula 2.PP/DD, considering normal values ≤ 0.44.

These variables were obtained from M mode echocardiography from the parasternal short-axis view plane on two-dimensional echocardiography at the level of the papillary muscles of the mitral valve, with intra and interobserver variability of 5 and 10%, respectively. By doppler echocardiographic analysis in the apical 5-chamber place, using continuous Doppler, we determined peak velocity of blood flow in the aortic root. Through the modified Bernoulli formula, we calculated the maximum valve gradient, from which the severity of aortic stenosis was quantified. We considered gradient ≤ 30 mmHg as mild stenosis; moderate, between 30 and 50 mmHg; severe above 50 mmHg.

Patterns of ventricular remodeling
Based on the values of relative wall thickness and myocardial mass, patients were classified into 4 patterns of left ventricular geometry: normal geometry, RWT <0.44 and MM ≤ 224 and 162 g (for men and women, respectively); concentric remodeling, RWT > 0.44 and MM ≤ 224/162 g; concentric hypertrophy, RWT > 0.44 and MM > 224/162 g; and eccentric hypertrophy, RWT < 0.44 and MM > 224/162 g.

Statistical analysis
Statistical analysis was performed using the statistical package SAS for Windows version 9.2. The data were presented as means and standard deviations. Comparisons between groups were made by chi-square test. In multivariate analysis, we adjusted a logistic regression model to explain the presence of hypertrophy. In all analyses, the significance level p < 0.05 was considered.

Results
Out of the 298 studied patients with aortic stenosis, 48% had a history of hypertension and had been treated pharmacologically. We observed that at the three levels of aortic injury, i.e., mild, moderate and severe, the left ventricular mass was greater in AoS associated with hypertension than in isolated AoS (mild AoS: 172 ± 45 vs 223 ± 73 g; p < 0.0001; moderate AoS: 189 ± 77 vs 245 ± 81 g; p = 0.0313; severe AoS: 200 ± 62 vs 252 ± 88 g; p = 0.0372) - Table 1. We also noted that in patients with AoS, the presence of hypertension was associated with increased risk of LVH (OR = 2.1; 95%CI: 1.2 to 3.6; p = 0.012) and that, considering all patients, LVH was more prevalent in females (OR = 2.7; 95% CI 1.6 to 4.5, p = 0.0002).

As to geometric remodeling, concerning the 4 patterns (normal, concentric remodeling, eccentric hypertrophy and concentric hypertrophy), we observed that in mild AoS without hypertension, there was a clear prevalence of normal LV geometry (50% of cases), and with hypertension, there was the predominance of concentric hypertrophy (48% of cases). In moderate AoS without hypertension, the prevalence was concentric hypertrophy (50% of cases); with the presence of hypertension, although the number of cases with concentric hypertrophy has been the most prevalent (40%), a significant percentage of patients had eccentric hypertrophy (32%). When we analyzed the patients with severe AoS without hypertension, we observed that the percentage of cases with concentric hypertrophy and concentric remodeling was similar (31 and 28% respectively), a different behavior from that observed in AoS with severe hypertension, which had clear predominance.

Table 1 - Left ventricular mass (VM) (g)

<table>
<thead>
<tr>
<th></th>
<th>Hypertension</th>
<th>Mean</th>
<th>sd</th>
<th>Median</th>
<th>Q1</th>
<th>Q3</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild AoS</td>
<td>No</td>
<td>172.73</td>
<td>45.5</td>
<td>164.74</td>
<td>137.07</td>
<td>200.50</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>223.55</td>
<td>73.17</td>
<td>213.26</td>
<td>168.85</td>
<td>261.83</td>
<td></td>
</tr>
<tr>
<td>Moderate AoS</td>
<td>No</td>
<td>189.97</td>
<td>77.32</td>
<td>174.54</td>
<td>161.33</td>
<td>193.45</td>
<td>0.0313</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>245.76</td>
<td>81.31</td>
<td>217.40</td>
<td>191.33</td>
<td>304.88</td>
<td></td>
</tr>
<tr>
<td>Severe AoS</td>
<td>No</td>
<td>200.59</td>
<td>61.68</td>
<td>194.38</td>
<td>151.30</td>
<td>220.26</td>
<td>0.0372</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>252.20</td>
<td>88.18</td>
<td>233.75</td>
<td>187.54</td>
<td>309.56</td>
<td></td>
</tr>
</tbody>
</table>

AoS - aortic stenosis; sd - standard deviations.
Hueb et al
Aortic stenosis and hypertension

Original Article

of cases with concentric hypertrophy (68% of cases). Thus, the percentage of patients with concentric hypertrophy, in the subgroup with severe AoS, jumped from 28% to 68% (p = 0.013) when there was concomitant hypertension - Charts 1 and 2.

Discussion

In aortic stenosis, especially the severe one, in most cases blood pressure is expected to be low or normal due to low cardiac output due to reduced flow through the aortic valve. In our study, we found a hypertension prevalence of 48% in the population of patients with AoS at all levels, detected on echocardiography. These findings are different from those found by Antonini-Canterin et al whose prevalence of hypertension in their sample was 32%. This difference can be explained bearing in mind that all patients in that study were symptomatic patients with severe AoS, therefore, with a smaller less possibility of high blood pressure.

Hypertension and aortic stenosis represent two different models of chronic pressure overload and both can lead to the development of left ventricular hypertrophy, with different patterns of ventricular geometry identified by echocardiography, i.e., concentric remodeling, concentric hypertrophy and eccentric hypertrophy, which differ among themselves as for the cardiovascular risk.

Patients with hypertension often have abnormal left ventricular geometry, and this has been independently associated with adverse cardiovascular outcomes. Likewise, the aortic valve stenosis, by itself, also alters LV geometry, and its association with hypertension may increase the ventricular mass and change its geometry in order to establish a cardiovascular risk higher than expected for isolated AoS. In untreated mild to moderate hypertension, the prevalence of ventricular hypertrophy on echocardiography was 30 to 50%, and the most common patterns of ventricular abnormalities were: concentric remodeling and eccentric hypertrophy. Koren et al evaluating the prognosis of hypertension in a prospective cohort study with 280 patients, found that hypertension was independently associated with cardiovascular events, and the higher the ventricular mass, the higher cardiovascular mortality. When ventricular geometry was considered, a cardiovascular event occurred in 11% of patients with normal geometry, 15% with concentric remodeling, 23% with eccentric hypertrophy and 31% in those with concentric hypertrophy.

Rieck et al analyzed the SEA study and found that, in asymptomatic patients with AoS, the presence of hypertension influenced ventricular geometry and was associated with increased myocardial mass and relative wall thickness. Nevertheless, most patients with AoS and hypertension had normal ventricular geometry (59%); in those with abnormal geometry, the pattern of remodeling was similar in both situations (with and without hypertension), and eccentric hypertrophy was the most common one (21% with hypertension and 19% without hypertension). Concentric remodeling and concentric hypertrophy were found at a lower frequency (8% in both situations). In a mathematical simulation model. Garcia et al reported that in mild and moderate AoS,
the concomitance of hypertension would have an important role in the development of LVH and hypertension would have a greater impact than AoS in the change in ventricular geometry. In the severe AoS, the impact of hypertension would be little significant.

In our data, hypertension was very important in the magnitude of ventricular mass in patients with mild and moderate AoS and less relevant in patients with severe AoS. Likewise, absence of hypertension in patients with AoS, at all levels, exerted a protective effect for the presence of LVH (OR = 0.272; p < 0.0001). When we analyzed the entire sample, we observed that the presence of LVH was more prevalent in female patients, therefore, women were 2.7 times more likely to have LVH than men. These findings are consistent with previous studies that have shown that females are more related to LVH than men in conditions of increased LV afterload. 

In patients with severe AoS, concentric hypertrophy has been reported as the most common pattern of ventricular geometry regardless of the presence or absence of hypertension. Antonini-Canterin et al. evaluated LV geometry in 193 consecutive patients with symptomatic severe AoS, of which 32% had hypertension, and identified concentric hypertrophy in 50% of patients with AoS associated with hypertension, and in 50% of those with AoS without hypertension. Eccentric hypertrophy was found in 29% of patients with AoS associated with hypertension and 31% without hypertension. Concentric remodeling was found in 15% in both groups. Therefore, in this study, hypertension did not influence ventricular geometry in patients with severe AoS. By analyzing our data, we can observe that most patients with AoS without mild hypertension showed normal left ventricular geometry, and in the presence of hypertension, concentric hypertrophy was the most prevalent one (48%).

Compared to patients with moderate AoS, the 04 models of ventricular remodeling had a similar prevalence in cases with and without hypertension. On the other hand, by assessing patients with severe AoS, it was found that in the situation where there was no association with hypertension, the prevalence of 04 patterns of ventricular geometric were equivalent and in those with hypertension, there was a clear predominance of cases with concentric hypertrophy, which is the pattern of ventricular geometry mostly associated with adverse cardiovascular events.

Our findings show that, in aortic stenosis, hypertension increased myocardial mass, which would theoretically increase the cardiovascular risk and adversely change ventricular geometry. In some way, these results highlight the importance of treating hypertension in patients with AoS. But there is a series of controversies involved in the administration of antihypertensive drugs in patients with AoS, which is why they have been classically contraindicated in this situation. The reason for this is that with a fixed obstruction of the LV outflow tract, reduction of systemic vascular resistance is not followed by a proportional increase in cardiac output. Thus, excessive vasodilation can cause reduced coronary blood flow and cerebral perfusion pressure and may result in symptoms of angina, syncope and even sudden death; the latter, caused by limited coronary flow determined by AoS.

On the other hand, pressure and volume overload caused by aortic valve disease increases levels of cardiac angiotensin-
converting enzyme and may contribute to increased collagen I and III and messenger RNA\textsuperscript{18}, thereby angiotensin-converting enzyme inhibitor drugs could be useful in this situation.

Likewise, it is believed that reducing blood pressure in hypertensive patients with aortic stenosis would cause ventricular mass reduction which would theoretically reduce cardiovascular risk. Furthermore, hypertension can be an aggravating factor in the progression of aortic stenosis, and its control is important to slow down the progression of valve disease\textsuperscript{19}. Tuseth et al\textsuperscript{20} found that hypertension is associated with a greater presence of asymmetric septal hypertrophy in patients with asymptomatic aortic stenosis, regardless of the severity of the stenosis, a condition that worsens the prognosis of surgery.

Finally, it is worth emphasizing that the severity of aortic stenosis may be masked by the coexistence of hypertension (underestimated valve gradient); thus, the degree of AoS should be interpreted with caution when blood pressure is high and should be reassessed after the normalization of pressure\textsuperscript{21}. Thus, despite the classic contraindication for patients with severe AoS, antihypertensive drugs should be considered when treating these patients when hypertension is associated with AoS.

**Conclusion**

In patients with AoS, the presence of hypertension was an additional factor of increased left ventricular mass, also interfering with ventricular geometry. These findings were relevant and of clinical importance in cases of severe AoS, in which hypertension contributed to increased myocardial mass and clearly influenced the pattern of ventricular geometry, resulting in a greater prevalence of concentric hypertrophy.

**Potential Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

**Sources of Funding**

There were no external funding sources for this study.

**Study Association**

This study is not associated with any post-graduation program.

**References**

3. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass to geometry and morbidity in uncomplicated essential hypertension. Am Intern Med. 1991;114(5):345-52.
4. Lang RM, Bierq M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18(12):1440-63.