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Load independent impairment of reverse remodeling after valve replacement in hypertensive aortic stenosis patients

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ABSTRACT

Background: We evaluated the impact of hypertension on the left ventricular mass regression in aortic stenosis after aortic valve replacement.
Methods: We prospectively studied 135 patients with severe aortic stenosis at baseline and 1 year after surgery. In 32 patients we analyzed myocardial gene expression of collagen types I and III, connective tissue growth factor, transforming growth factor-β1, metalloproteinase-2 and its tissue inhibitor and compared its levels vs controls.
Results: Seventy-six patients (56.3%) had a history of hypertension. Hypertensive patients were older, had higher Euroscore-II and NYHA class, with no differences in stenosis severity. At 1 year follow-up there was a median decrease of mass index of 14.2% (P25–75: −4.3%–30.4%; $p < 0.001$). Mass regression was significantly higher in patients without hypertension, with a median decrease of 25.9% (P25–75: 12.0%–38.7%) vs 5.4% (P25–75: −12.5%–20.1%; $p = 0.001$), despite similar increase in effective orifice area and no differences in valvuloarterial impedance. After 1 year, higher baseline left ventricular mass index ($p = 0.005$) and the absence of hypertension ($p = 0.002$) or diabetes ($p = 0.041$) were the only independent predictors of mass regression higher than the median. Comparing with controls, aortic stenosis patients had an increased expression of collagen types I and III, but only hypertensive patients had higher relative expression of collagen type I vs III. In hypertensive patients TIMP2 expression was up-regulated and correlated with higher baseline left ventricular mass index ($r = 0.61$; $p = 0.020$).
Conclusions: In aortic stenosis, hypertension impairs mass regression one year after valve replacement, independently of total afterload. Differences in the expression of extracellular matrix remodeling genes might contribute to this finding.

1. Introduction

Hypertension (HT) is a common comorbidity in patients with aortic valve stenosis (AS), with a previously reported prevalence of 33–72% [1–4].

In chronic pressure overload states, like systemic HT and AS, the left ventricle (LV) responds with hypertrophy and altered geometry as an adaptative mechanism that helps to maintain contractile performance despite abnormal loading conditions. LV hypertrophy (LVH) allows for normalization of systolic wall stress and has been considered as compensatory [5], but it is also associated with impaired coronary blood-flow reserve [6] and changes in cardiomyocytes and extracellular matrix (ECM) connective tissue, some of them irreversible [7]. Moreover, the presence of residual hypertrophy after aortic valve replacement (AVR) has been associated with incomplete recovery of left ventricular function and worse prognosis [8–10].

The coexistence of hypertension and valvular aortic stenosis (AS) is common, but few studies have assessed the impact of concomitant hypertension on LV structure and function in patients with AS. Moreover, although we have evidence of changes in the composition and structure of ECM in the progression to heart failure in AS [11] and HT [4], there is no published data comparing the expression of genes regulating ECM production in patients with both types of pressure overload.

Therefore our aim was to evaluate the importance of HT on LV remodeling and LV mass regression in AS patients one year after AVR.

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Additionally, we did a subgroup analysis on myocardial expression of genes involved in ECM remodeling in aortic stenosis patients with and without HT, and compared its results with those of a control group.

2. Methods

2.1. Patient selection and follow-up

Between January 2006 and December 2009 we included 141 consecutive patients over 18 years old with severe symptomatic AS (aortic valve area < 1 cm^2 or mean transaortic gradient ≥ 40 mm Hg) referred for aortic valve replacement (AVR) at the Cardiothoracic Surgery Department of Hospital São João, Porto, Portugal. This investigation conforms to the Declaration of Helsinki, had institutional ethical review board approval and each study participant signed an informed consent before enrolment. We excluded patients with aortic regurgitation >II/IV or other significant valve diseases (>mild), and significant coronary artery disease (lesions > 50% on coronary angiography). All patients were in sinus rhythm at the time of inclusion for a more accurate evaluation of diastolic function parameters. From the initial 141 patients, 135 were considered for this prospective analysis: one was refused for surgery, other died before surgery from cholangitis with sepsis, and there was incomplete clinical data in four of them. One year clinical and echocardiographic follow-up was achieved in 91 (67.4%) patients. The remaining patients were not lost to follow-up, except for two cases, but had echocardiographic evaluation at 6 months or beyond 1 year and those values were not considered. The diagnosis of hypertension was considered whenever it was registered in the clinical records of the assistant physician. Renal insufficiency was determined when estimated glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 by the Cockcroft–Gault formula and perioperative renal failure if there was an increase in serum creatinine >25% the preoperative value. Medical therapy was at the discretion of assistant physician.

Given the shortage of human myocardial samples in normal adults, for the control group of the molecular substudy we recruited nine mitral stenosis (MS) patients without coronary artery disease or significant mitral regurgitation and/or aortic valve disease. These patients had no significant left ventricular overload and should have a local expression of ECM genes more similar to the normal left ventricles.

2.2. Surgical technique and biopsies

All surgeries were performed using standard procedure for aortic or mitral valve replacement. The patients were placed on cardiopulmonary bypass and cardiac arrest was induced and maintained with cold blood cardioplegia. The majority of patients received a bioprosthesis (73.3%). Two patients also had ascending aorta aneurism and underwent aortic root replacement with valved composite grafts (Bentall technique). In 32 patients with AS myocardial biopsies were procured at the time of surgery from the LV interventricular septum. In 9 mitral stenosis patients undergoing mitral valve replacement, excised papillary muscles were collected and used as control myocardial biopsies. In both cases, excised myocardium was immediately snap-frozen in liquid nitrogen and stored at −80 °C.

2.3. Echocardiographic studies

Echocardiographic examination was performed by a trained cardiologist and recorded on digital support. All recordings were examined by an experienced echocardiographer in an accredited independent echocardiography laboratory (Hospital Clínico San Carlos in Madrid, Spain) blinded to patient details. Studies were performed using Phillips IE-33 equipment with a S5-1 transducer and M-mode, two dimensional, pulsed, continuous, color-flow and tissue Doppler capabilities. Correct orientation of imaging planes, cardiac chamber dimension, function measurements, LV mass index and relative wall thickness were performed according to the European Association of Echocardiography (EAE)/American Society of Echocardiography (ASE) recommendations [12]. LV mass index greater than 115 g/m2 in men and greater than 95 g/m2 in women was considered indicative of LV hypertrophy. LA volume was measured in LV end systole in the frame preceding mitral valve opening, using the biplane area length method and corrected for body surface area. To evaluate systolic function we used LV ejection fraction (EF), estimated using Simpson's biplane method, and longitudinal systolic function, assessed by peak systolic mitral annular motion.

Aortic valve area was estimated using quantitative Doppler by continuity equation. Mitral inflow by pulsed wave Doppler and septal e′ tissue Doppler velocity of the mitral annulus were obtained from the apical 4-chamber and according to ASE guidelines [13]. Patients with an E/e′ septal >15 were considered to have increased filling pressure, whereas patients with E/e′ septal <8 were considered to have normal filling pressure. In the remaining patients with an indeterminate E/e′, those with LAVi ≥34 ml/m^2 were considered to have increased filling pressure. The presence of increased filling pressures was considered indicative of diastolic dysfunction.

Peak wall stress (WS) was estimated using a previously validated formula: $WS = 0.8 \times [0.334 \times (SAP + MaxG) \times LVID] / [PWTd \times (1 + (PWTd / LVID)] - 2(\times 10^3\ dyn/cm^2)$, where SAP = systolic arterial pressure, MaxG = maximal transvalvular pressure gradient, LVID = LV internal diameter, and PWTd = posterior wall thickness in diastole [14]. As a measure of global LV load, we calculated the valvuloarterial impedance: Zva = (SAP + MG) / SVI, where SAP = systolic arterial pressure, MG = mean transvalvular pressure gradient and SVI = stroke volume index. Blood pressure was measured before echocardiography with patients in supine position, and a mean of 3 measurements was considered.

2.4. mRNA quantification

For gene expression evaluation, RNA was extracted with TriPure (Roche) according to the manufacturer's instructions. RT-PCR was performed with total RNA, followed by real time PCR analyses using the SYBR Green method, in a LightCycler 2.0 (Roche) as previously described [15]. Results are normalized for GAPDH and expressed in arbitrary unit. Specific PCR primer pairs for the studied genes are displayed in Supplementary material.

2.5. Statistical analysis

Categorical variables were expressed as percentages and continuous variables as mean ± standard deviation or median and interquartile range, according to their distribution. Continuous variables were compared between groups using an unpaired *t*-test (for normally distributed variables) or the Mann–Whitney *U*-test (for non-normally distributed variables). For comparison between baseline and follow-up a paired Student's *t*-test was applied (normally distributed variables). Chi-square test was used to compare proportions. Spearman's rank correlation was used for the assessment of correlations between LVM index and its variation and clinical, echocardiographic and molecular continuous variables. Following univariate analysis, a stepwise binary logistic multivariate regression model (Wald backward stepwise method, $p = 0.05$ for covariate inclusion and 0.2 for exclusion) was performed (including potential confounders) for LVM index regression analysis 1 year after AVR (relative LVM index regression variable was dichotomized according to its median value: ≤14% (no LVM index regression or regression below median value) and >14% (LVM index regression higher than the median).

All reported probability values are two-tailed, and $p < 0.05$ was considered statistically significant. Analyses were performed with the IBM®SPSS® Statistics software package (version 19.0) (SPSS Inc, Chicago, IL, USA).

3. Results

Demographics and clinical parameters of the 135 patients with severe symptomatic AS are described in Table 1. Heart failure was the most prevalent presentation feature (81.5%), 72 (53.3%) patients had echocardiographic evidence of LV diastolic dysfunction and most patients had LVH (68.1%) with a mean LVM index of 129.6 ± 34.0 g/m^2 (Table S1, Supplementary data). Ninety nine cases (73.3%) had a bioprosthesis implanted (size 21 mm: 46.6%; 23 mm: 27.4%; 25 mm: 14.8%; 19 mm: 10.5%; and 17 mm: 0.7%). The median time of hospitalization was 6.0 days (P25–75: 6.0–8.0 days) and 2 hospital deaths occurred (1 from pneumonia and 1 due to stroke). At 1 year follow-up, there was an increase in the EOA index, decrease in valvuloarterial impedance and peak wall stress (Table S1), and a significant median decrease in LVM index of 20.6 g/m^2 (P25–75: −5.1 g/m^2–40.7 g/m^2) with a median relative decrease of 14.2% (P25–75: −4.3%–30.4%; $p < 0.001$).

Clinical and echocardiographic comparison between patients with (HT + AS) and without HT (ASwHT) are described in Tables 1 and 2. Hypertensive patients were older, had higher surgical risk and were in higher NYHA class. However there were no differences in AS severity.

One year after aortic valve replacement LVM regression was significantly higher in ASwHT, with a median decrease of 25.9% (P25–75: 12.0%–38.7%) vs 5.4% (P25–75: −12.5%–20.1%) in HT + AS ($p = 0.001$). In ASwHT only 25.6% had LVH at 1 year follow-up, but, in the presence of associated HT, 56.2% had persistent LVH ($p = 0.003$). At this time-point, patients with HT + AS had higher LVM index (118.9 ± 35.2 vs 101.0 ± 31.3 g/m^2; $p = 0.042$) when compared with ASwHT, despite similar increase in effective orifice area and similar prosthetic gradients (Table 2). LV reverse remodeling at 1 year was only significant in ASwHT (Fig. 1), with a decrease in LV end-diastolic (92.3 ± 33.0 vs 80.5 ± 29.8 ml, $p = 0.019$) and end-systolic (37.2 ± 23.0 vs 28.8 ± 12.3 ml, $p = 0.004$) volumes and relative wall thickness (0.48 ± 0.09 vs 0.45 ± 0.08, $p = 0.048$), with no change in indexed LA volume (Table 2). In HT + AS there was an increase in LA volume index, although there were no significant changes in estimated LV filling pressure (Table 2). As expected, there was a trend for higher systolic blood pressure in hypertensive patients (137.6 ± 18.8 vs 130.2 ± 17.1 mm Hg; $p = 0.069$), but there were no differences in valvuloarterial impedance (5.30 ± 1.60 vs