Myocardial Fibrosis and Ventricular Remodeling in Severe Chronic Aortic Regurgitation

Nelson Elias, Flávio Tarasoutchi, Guilherme Sobreira Spina, Roney O. Sampaio, Pablo M.A. Pomerantzeff, Francisco Rafael Laurindo, Max Grinberg

Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP - Brazil

Summary

Background: Significant symptomatic chronic aortic regurgitation (AR) leads to considerable left ventricular remodeling at the expense of myocyte hypertrophy and extracellular matrix remodeling. The relevance of interstitial fibrosis concentration in these patients is unknown. We analyzed the degree of fibrosis in the left ventricle (LV) in symptomatic patients with AR submitted to surgical treatment, and its relationship with functional and anatomical characteristics.

Objective: To evaluate myocardical fibrosis in chronic severe aortic regurgitation.

Methods: Twenty-eight patients with chronic symptomatic AR (16 with normal LV function and 12 with LV dysfunction) were selected and assessed pre- and postoperatively by echocardiography. Functional capacity was measured using maximal oxygen consumption (VO_2max) through the cardiopulmonary test. Myocardial fibrosis volume fraction (MFV) was quantified through endomyocardial biopsy performed in all patients during surgery. We compared the histopathologic results with a nine-patient control group.

Results: The mean age was 39 ± 12 years, 75% of the patients were male, and the rheumatic etiology accounted for 84% of the cases. Twenty-five patients remained in FC I and II at the end of the study, and there was a significant reduction of the LV diameters between the preoperative and late postoperative timepoints. Three deaths occurred but they were not related to postoperative ventricular dysfunction. The parameters of the cardiopulmonary test were similar between pre- and postoperative timepoints. MFV in patients with AR was significantly higher than in the control group (3.47 ± 1.9% *vs* 0.82 ± 0.96%, respectively, p=0.001). There was no statistical correlation among LV fibrosis and LV diameters, LVEF and MVO_2.

Conclusion: In patients with significant symptomatic AR, the presence of limited myocardial fibrosis was not associated with clinical, echocardiographic or functional complications. (Arq Bras Cardiol 2009;92(1):61-64)

Key words: Endomyocardial fibrosis; aortic valve insufficiency; ventricular function left.

Abbreviations

AR - Chronic aortic regurgitation.
MFV - Myocardial fibrosis volume.
FC - Functional class.
LV - Left ventricle.
LVDd - Left ventricular diastolic diameter.
LVSd - Left ventricular systolic diameter.
LVEF - Left ventricular ejection fraction.
VO_2max - Maximal oxygen consumption.
NYHA - New York Heart Association.
AVR - Aortic valve replacement.

Mailing address: Guilherme Sobreira Spina •
Av. Dr. Eneas de Carvalho Aguiar, 44 - Unidade Clínica de Valvopatia, Cerqueira César, 05403-000, São Paulo, SP - Brazil
E-mail: guilherme.spina@incor.usp.br
Article received on January 7, 2008; received revised on February 21, 2008; accepted on April 1, 2008.

Introduction

The natural history of chronic aortic regurgitation (AR) is characterized by a long asymptomatic period during which significant eccentric LV hypertrophy develops, as well as remodeling in response to volume-pressure overload[1].

Symptoms generally occur as a collapse of the LV adaptation mechanisms, and occasionally may result in permanent injury to the structure and function of the cardiomyocytes and changes in the extracellular matrix[2]. The extent of the injury may be such that LV function may be incapable of returning to normal, even after aortic valve replacement[3,4].

Over the two last decades[5,6], clinical trials were based primarily on LV dimensions and systolic function as indications of the ideal timing for aortic valve replacement. This procedure interrupts the natural history of AR, but it exposes the patient to the risks of surgery and valve prosthesis implantation. Up until now, there is still controversy as to the optimum time to interrupt the disease's natural history.

Many of the indexes available are based on measurements

of the left ventricular function, which depend much more on the pre- and post-overload than on LV contractility itself. However, the extracellular matrix is a significant component of the LV mechanism of adapting to the volume-pressure overload. The impact of how to interpret the accumulation of fibrosis on clinical, structural and functional parameters is unknown[7]. This information may help to improve and stratify prognostic indexes. Our aim was to assess the level of LV fibrosis in patients with AR and its correlation with functional and anatomical parameters.

Methods

Study population

AR patients with indications for surgery were prospectively selected according to modified Spagnuolo et al[8] criteria.

Patients aged < 18 or > 60 years, who had atrial fibrillation, with any other cardiac problems except AR, were excluded. All patients signed informed consent term forms, and the research project was approved by the scientific and research ethics committees.

Patients were evaluated by clinical and laboratorial criteria, and cardiopulmonary stress testing.

Clinical assessment

It consisted of three timepoints for each patient: 1) preoperative assessment (baseline), 2) early postoperative (1 month after surgery), and 3) late postoperative (8 to 12 months after surgery).

At each timepoint, echocardiographic and laboratory evaluations were performed. Most patients were medicated with digitalis, diuretics and angiotensin converter enzyme inhibitors during the preoperative phase. All patients underwent thorough evaluations as to etiopathogeny and symptoms such as angina, syncope, dizziness and NYHA functional class.

Echocardiography

Interpretation was based on the recommendations of the American Society of Echocardiography[9]. The following items were assessed by Simpson's method: LV diastolic diameter (LVDd), LV systolic diameter (LVSd), and LV ejection fraction (LVEF). Patients were divided into two groups: LVEF > 0.55 (normal) and LVEF < 0.55 (left ventricular dysfunction).

Cardiopulmonary stress testing

This was performed in a Cardio O_2 (Medical Graphics Corporation) cycle ergometer with a Hans-Rudolf # 2600 valve and 100ml dead space. The ramp protocol was set with a load adjusted according to each patient's physical exercise capacity so as to obtain approximately 10 minutes of workout. This enabled measurement of the maximal oxygen consumption (VO_2max)[10].

Collagen morphometry and histological analysis

Endomyocardial biopsy of the lateral LV wall was performed in all patients during surgery. This area was selected for biopsy because it has no conduction bundle.

The incision was carefully performed, always by the same surgeon, with a # 11 scalpel blade, in order to obtain 3mm depth and 6mm length.

Tissue fragments were fixed in 10% formaldehyde and later embedded in paraffin. Serial 5mm sections were mounted onto labeled slides and stained with Masson's trichrome for detection and quantification of collagen, and with hematoxylin-eosin for histological analysis. The fractions of myocardial fibrosis volumes (MFV) were quantified by video-morphometry using an image analysis system (Quantimet 520 Image Analysis System-Cambridge Instruments, Cambridge, UK). The quantification of the MFV fraction was calculated as the ratio of the area positively stained for fibrosis to the total myocardial area. The endocardium was not considered. Measurements were made on the serial sections, in all fields observed with 10X optical microscopy. In order to compare the histopathological results, a nine-patient (mean age 27 ±16 years) control group was assembled; three of them died of non-cardiac causes and their hearts had normal aspects. Myocardial biopsy samples were taken from the LV lateral wall. Calculation of the myocardial fibrosis volume (MFV) was made using methodology with Masson's trichrome and video-morphology previously mentioned.

Statistical analysis

Statistical analysis was performed using the SAS software. The statistical significance was set as 0.05. Continuous variables were expressed as mean ± standard deviation (SD), whereas the categorical variables were expressed as absolute and relative frequencies. Paired and non-paired T tests were used. Qualitative data were analyzed using the ratio equivalence hypothesis, the chi-square test or, when the number was limited, Fisher's exact test. Multivariate analysis of the profile was used to analyze the echocardiographic changes occurred during the follow-up.

Results

We analyzed 28 patients who had undergone aortic valve replacement, with a mean age of 39±12 years, 75% of them male, and 84% with rheumatic etiology. At the end of the study, twenty-five patients were in functional classes I and II. Three patients died, one of them on the 5th postoperative day due to aortic rupture, and the other two during the 4th and 9th postoperative months due to infectious endocarditis.

There was a significant reduction in left ventricular diameters between the preoperative and the late postoperative timepoints (Table 1). LVEF and cardiopulmonary stress test data were similar between the two timepoints (pre- and late postoperative).

All AR patients had a high content of fibrosis relative to the control group. MFV in patients with AR was 3.47±1.9%, compared to 0.82±0.96% in the control group (p=0.001).

Figures 1, 2 and 3 show no correlation between the grade of fibrosis and the left ventricular diameters, left ventricular function, and VO_2max.

Sixteen patients had LVEF >0.55, and 12 patients had LVEF

Table 1 - Pre- and late postoperative behaviour of laboratory tests

Variables	Preoperative 28 patients	Postoperative 26 patients	P
LV diastolic diameter (mm)	76.85 ± 7.20	64.42 ± 12.15	0.0001
LV systolic diameter (mm)	55.92 ±10.07	48.19 ± 13.99	0.0034
LV ejection fraction (%)	0.60 ± 0.15	0.58 ± 0.14	0.4000
Shortening fraction	0.30 ± 0.16	0.28 ± 0.16	0.4364
O_2 consumption (ml/min)	1458 ± 754	1507 ± 660	0.5182
Predicted O_2 consumption (%)	62 ± 22	64 ± 19	0.5740
Predicted maximum potency (%)	11.69 ± 3.32	12.62% ± 2.60	0.0560

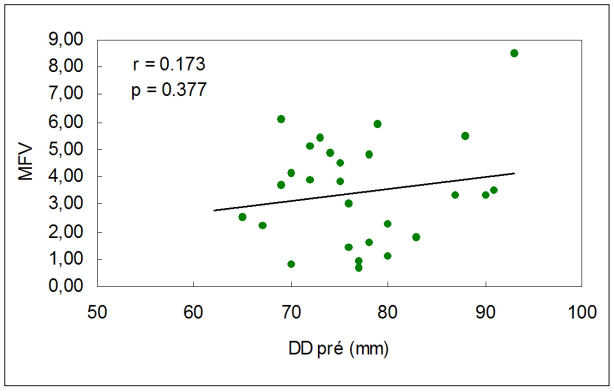

Figure 1 - Correlation between Myocardial Fibrosis Volume (MFV %) and diastolic diameter (DD).

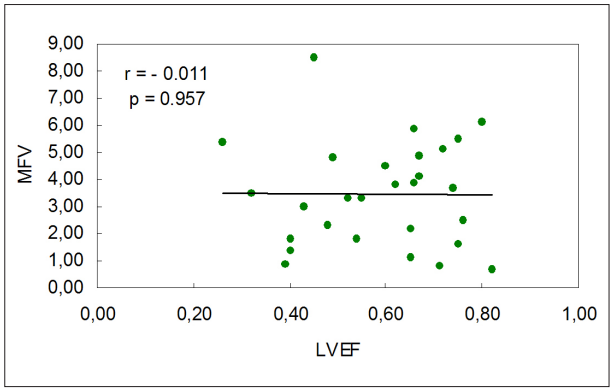

Figure 2 - Correlation between left ventricular ejection fraction (LVEF) and Myocardial Fibrosis Volume (MFV %).

<0.55. The mean age of patients with a normal LVEF (35±11 years) was lower than that of the group with LV dysfunction (45±11 years, p=0.02). There was no significant difference of MFV between the groups with and without LV dysfunction (3.52±1.82% *vs* 3.33±2.10%, respectively, p=0.799).

Discussion

AR patients may have a difficult follow-up, as the frequent morphological changes do not correlate with clinical symptoms[4,11]. Over the past two decades, a few parameters

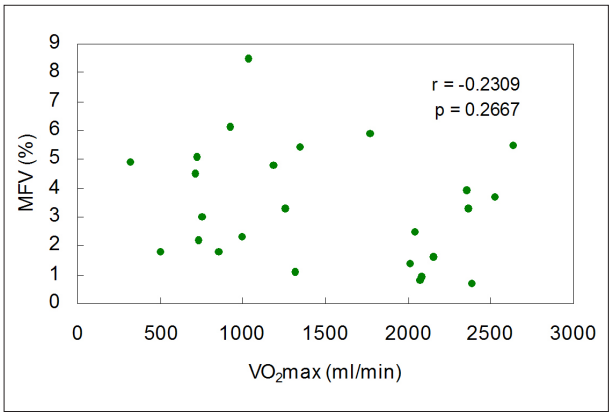

Figure 3 - Correlation between the Myocardial Fibrosis Volume (MFV %) and the Maximal Oxygen Consumption (VO_2max ml/min).

emerged such as LVDd >70mm, LVSd >55mm, and shortening fraction ≤ 0.25, which indicated poorer postoperative results. However, studies on the correlations between the reduction in ejection fraction, increase in left ventricular diameters, and myocardial fibrosis in AR are scarce.

Fibrosis is a restrictive element in LV remodeling. The patient may benefit from surgery through the reduction of volume-pressure overload and the resulting improvement in contractility. Nevertheless, the degree of established fibrosis may determine an incomplete regression of left ventricular remodeling, especially from a viscoelastic point of view. During the adaptive hypertrophy phase, there is an increase of more elastic forms of collagen that maintain the LV relatively compliant, despite the increased muscle mass[12]. Myocardial fibrosis is an important prognosis marker in heart failure. In our study, however, we were not able to detect a correlation between myocardial fibrosis and left ventricular function, probably due to the significant degree of left ventricular hypertrophy even in the presence of ventricular dysfunction.

The magnitude of the myocardial fibrosis volume (MFV) in our patients was 3.47%, smaller than the 4.97% value identified in the cases of idiopathic dilated cardiomyopathy[13]. In hypertensive cardiomyopathy, the value reported was even higher (approximately 8.50%)[13], similar to that found in alcoholic cardiomyopathy (10.77%)[14]. In our study, the normal MFV value in the control group was 0.82%. Paradoxically, the worst prognosis in the groups abovementioned was reported in the cases of idiopathic dilated myocardiopathy, precisely the group with the smallest quantity of myocardial fibrosis. Our results, along with the data above, indicate that fibrosis does not seem to be a determinant factor for the prognosis of myocardial diseases.

With our study, we can speculate that the interstice does not necessarily reflect the degree of left ventricular dysfunction, a fact asserted by some authors[12,15] in other series of AR patients. An important datum in our group of patients is the predominance of young rheumatic individuals (84%, with a mean age of 39 years), which distinguishes this study from other studies in literature, where the age bracket is higher (approximately 55 years of age) and with predominant non-

rheumatic etiology[1,11]. Another possible explanation for such a discrepancy is that the level of ventricular impairment does not consist of collagen alone, but also of other non-collagen elements of the extracellular matrix, such as fibronectin[16].

The similar magnitude of fibrosis in both groups studied (3.52±1.82% in the group with no LV dysfunction *vs* 3.33±2.10% in the group with LV dysfunction, p=0.799) suggests that fibrosis is not an essential determinant in the natural history of AR. The absence of a correlation between the fibrosis and VO_2M also corroborates this theory.

Conclusion

Our conclusion is that in patients with significant chronic symptomatic aortic regurgitation submitted to surgery, myocardial fibrosis did not correlate with clinical and functional parameters, or left ventricular remodeling.

Therefore, in view of the complexity of the physiopathology, we continue to follow ventricular remodeling through clinical, laboratorial, and histopathological studies, since we have not found in medical literature a reliable laboratory parameter that may foresee prognosis.

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 article is part of the thesis of Doctoral submitted by Nelson Elias, from *Faculdade de Medicina da Universidade de São Paulo*.

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