Original Article

Correlation to NT-ProBNP and Remodeling after Cardiac Surgery

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Abstract

Background: **Few data are available on diastolic function in patients with aortic stenosis (AOS) with indication of surgical treatment. A potential correlation between biomarkers and diastolic function has not been established.**

Objective: **The aim of our study was to evaluate diastolic function in patients with AOS waiting for aortic valve replacement (AVR) echocardiographically, and to verify its correlation with serum brain natriuretic peptide (NT-proBNP).**

Methods: **Thirty-one AOS patients (11 male), 21 to 81 years old (mean age, 61±15 years old) were studied before and after AVR. Diastolic function was assessed with Doppler methods: transvalvar mitral flow, tissue Doppler imaging (TDI) and pulmonary venous Doppler (PVD), correlating with serum brain natriuretic peptide (NT-proBNP) before and 6 months after AVR.**

Results: **Comparing pre to post-operative period, we observed an increase of the left atrial ejection fraction and isovolumetric relaxation time (IRT), and the decrease of the mitral velocity to early diastolic velocity of the mitral annulus ratio (E/E'), the difference between the pulmonary A wave duration and mitral A duration, left atrial systolic volume, left atrial systolic volume index, left ventricular diastolic diameter, left ventricular systolic diameter, end diastolic volume (LVEDV), left ventricular mass index, left ventricular volume and mass index ratio. The values of NT-proBNP were positively correlated to diastolic dysfunction, both before and after surgery.**

Conclusion: **AOS patients' ventricular diastolic function improved after AVR. The biomarker NT-proBNP might be a useful biomarker of diastolic function in these patients, before and after AVR. NT-proBNP values show a positive correlation with echocardiographic variables that determine diastolic dysfunction, and is a good marker for the characterization of this dysfunction in AOS patients. (Arq Bras Cardiol. 2013; 100(5):469-475)**

Keywords: **Aortic Valve Stenosis / surgery; Ventricular Dysfunction; Natriuretic Peptide, Brain.**

Introduction

Left ventricle diastolic function is related both to its relaxation and filling. In general, it is quantified by Echo-Doppler[1-4].

An additional manner of evaluating cardiac function is by measuring the serum concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP). NT-proBNP levels are increased in patients with both systolic and diastolic LV dysfunction[5]. Januzzi et al[6] showed a correlation between NT-proBNP serum levels and prognosis in systolic heart failure.

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Manuscript received May 14, 2012, revised mnanuscript November 16, 2012, accepted December 17, 2012.

DOI: 10.5935/abc.20130076

However, NT-proBNP measurement cannot differentiate systolic from diastolic heart failure. Thus, NT-proBNP exerts an important role in the evaluation of diastolic dysfunction only when combined with echocardiographic evaluation.

Patients submitted to surgery for correction of aortic stenosis (AOS) present immediate improvement of systolic function. On the other hand, diastolic dysfunction remains and can ever worsen, since myocardial hypertrophy reversal occurs faster than interstitial fibrosis reduction[7-9].

As for LV mass increase, left atrial (LA) function can be considered a marker of diastolic dysfunction severity. Lubien et al[10] observed higher BNP levels when LA increase is combined to LV hypertrophy.

However, the relationship between biomarkers and LV remodeling, specifically in AOS patients submitted to aortic valve replacement has not yet been established[10-13] Some studies suggest that NT-proBNP can be used in diagnostic and prognostic applications. Fisher et al[14] observed that patients with congestive heart failure and higher than average NT-proBNP values had a 1-year mortality rate of 53%, as compared to a 11% rate registered for patients with lower than average values.

Biomarkers, particularly NT-proBNP, have not been accurately evaluated in AOS. The present study aims to analyze LV mass reduction and left atrial and ventricular remodeling in patients submitted to aortic valve replacement surgery due to significant AOS, as well as correlating NT-proBNP levels with various levels of diastolic dysfunction, both before and after surgery.

Methods

Study design

This is a longitudinal observational study of patients with significant AOS who have indication of surgical treatment.

Patients

Thirty-one NYHA class III or IV AOS patients (11 male) aged 21 to 81 years old (mean age, 61±15 years old) with preserved systolic function and indication of surgical treatment of the valvular heart disease were included.

Exclusion criteria

a) Severe coronary failure

b) Other moderate or severe valvular heart disease

c) Atrial fibrillation

Hypothyroidism, neoplasia, chronic renal insufficiency or severe chronic obstructive pulmonary disease.

Transthoracic echocardiography

The exams were carried out with the patient lying in the left side position, both 1 to 3 months before and 6 months after surgery. The equipment (HDI 5000 [Philips Medical Systems, Andover, MA, USA], with multi frequency electronic sector transducer, pulsed, tissue and continuous Doppler and colored flow mapping) used is commercially available. The patients were submitted to simultaneous electrocardiographic monitoring and the exams were performed according to the recommendations of the American Society of Echocardiography[15].

At least three measurements were obtained for each variable and the mean values were used for each one.

The echocardiographic variables used both in the pre- and postoperative periods were:

1- LV end-systolic diameter and end-diastolic diameter.

2- End-diastolic septal and LV posterior wall thickness, used for calculating LV mass index (according to Devereux formula)[15].

3- LV systolic function, calculated as LV ejection fraction (LVEF), according to Simpson rule (bidimensional measurement)[16].

4- Aortic valve area, calculated by the continuity equation[16].

5- LV diastolic function:

5.1 Pulsed Doppler study of the mitral transvalvar flow: mitral transvalvar flow was assessed at the apical four-chamber view, with the pulsed Doppler probe placed in the LV entry pathway, at the distal mitral valve leaflets, with 2-mm sample volume. The following parameters were evaluated:

5.1.a) Protodiastolic LV filling velocity (E wave), in cm/s.

5.1.b) Telediastolic LV filling velocity (A wave), in cm/s.

5.1.c) Telediastolic LV wave duration (A wave measured by pulsed Doppler), in ms.

5.1.d) Ratio between E and A wave (E/A)

5.1.e) LV filling flow deceleration time (DT), in ms.

5.2 Isovolumetric relaxation time (IVRT).

5.3. Pulsed Doppler study of pulmonary venous flow, evaluating the following parameters:

5.3.a) Pulmonary venous flow systolic component (S wave), in cm/s.

5.3.b) Pulmonary venous flow diastolic component (D wave), in cm/s.

5.3.c) Atrial wave contraction duration (A wave time), in ms.

5.3.d) Atrial contraction peak (A wave), in cm/s.

5.4. Tissue Doppler mitral ring study: the image was obtained by tissue Doppler at apical 2- and 4-chamber view, 1-2 mm sample volume.

The maximum myocardial displacement speed was measured at the beginning and at the end of diastole (E' and A' waves, respectively), and during systole (S' wave), at the septal, lateral, inferior, anterior and rings and the VD lateral ring[17,18].

LA volume was measured at apical 2- and 4-chamber view. LA systolic and diastolic volumes were measured for calculating LA emptying fraction, using a method similar to Simpson's[18].

Statistical analysis

A descriptive analysis was performed on the data obtained from the 31 patients, taking into account demographics, echocardiographic variables and NT-proBNP values before and after surgery.

The mean value found for each variable was compared among AOS patients, before and after surgery. For mean comparison, the Wilcoxon test was used since the variables do not follow a normal distribution, with the exception of the BNP logarithm (compared by the Student t-test).

Results

Study population

Thirty one patients (21 female; mean age 61±15 years old) with significant aortic stenosis were included.

AOS patients mean age was 61.5±14.72 years old (ranging from 21 to 81 years).

Of the study patients, 26 had atherodegenerative AOS, 4 had congenital AOS and 1 had rheumatic AOS.

Echocardiographic data

Improvement of echocardiographic parameters between the pre- and postoperative periods can be observed on analyzing data on Table 1.

Diastolic dysfunction and NT-proBMP correlation

Diastolic dysfunction improved between the pre- and postoperative periods, although values were not yet normal at the study period (Table 2).

NT-proBNP levels decreased postoperatively in comparison to the pre-operative period (Table 3). After classification in three levels (I, II and III), the sample was evaluated for the difference among the groups according to log-NT-proBNP value. ANOVA test showed significance between groups (F=3.850, p=0.027) and the Bonferroni post hoc test demonstrated a difference on log-NT-proBNP values between Grade I (mean 4.58) and Grade II (mean 4.69) (p=0.025). However, no statistically significance difference was found between Grades II (mean 4.69) and III (mean 4.70) on log-NT-proBNP values (p=0.08) (Table 4).

Using Pearson linear correlation and Spearman correlation, we have observed that the variables E/E', EF/LA, LA systolic volume, indexed LA systolic volume, LVSD, indexed LV mass and volume/mass ratio show a correlation with log-NT-proBNP (Table 5). The variables E/E', LA systolic volume, indexed LA systolic volume, LVSD and indexed LV mass show a positive correlation, indicating that NT-proBNP logarithm increases with increasing values of the respective variables. On the other hand, NT-proBNP logarithm decreases when the variables mitral A time-pulmonary A time, LAEF and volume/mass ratio increase.

The variables with significant Spearman and Pearson correlations are the same. The variables behavior is identical to the one observed previously, and NT-proBNP logarithm also increases with LVSD increase.

When verification is done on a logistic regression model (Table 6), the risk of diastolic dysfunction in a patient with log-NT-proBNP equal to 4.78 (BNP=119.10) is 92.01% [CI 955, 83.45%; 96.33%], the risk of diastolic dysfunction increases 2.64 times [CI 95%, 1.21; 5.78] for each 1-unit increase in log-NT-proBNP.

Discussion

The relationship between LV geometry in AOS and remodeling after aortic valve replacement is not known. In the early postoperative period, few patients present LV mass reduction, but 18 months after the procedure LV hypertrophy and end-diastolic volume decrease[19,20].

Mitral transvalvar flow velocity is an important parameter for evaluating filling pressures; however, it can be modified or influenced by various factors and the same is true for pulmonary venous flow. Tissue Doppler analysis and LA volume evaluation[21] were included in the present study for minimizing these limitations and increasing diastolic dysfunction diagnostic precision[21].

It was possible to verify an improvement of LAEF in the postoperative period (as compared to the findings before surgery), meaning an improvement in diastolic function after valve replacement surgery due to LV mass regression and adaptation of the heart to the new post-load values[22]. LA dilation follows LV diastolic dysfunction development and is an important predictor of adverse events, particularly arrhythmias. On the other hand, LA volume reduction and LAEF improvement suggest that reverse remodeling occurred, implying that cardiovascular risk was reduced.

Indexed LV mass reduction, in turn, is also a strong (and the most consistent) predictor of events after valve replacement surgery, independently from gender, age and valve replacementtype[23].

According to the *European Society of Cardiology*[11], besides considering the symptoms of HF with normal LVEF, diastolic HF can be diagnosed by tissue Doppler (on which E/E' ratio is essential), combined with evaluation of mitral transvalvar flow and pulmonary venous flow by pulsed Doppler. LV mass index and LA indexed volume corroborate the diagnosis. Nagueh et al[24] showed that, in patients with preserved LVEF, E/E' ratio is 8 to 15 and that other measurements are required for diagnosing diastolic dysfunction. We must now highlight that, despite the applicability of diastolic function evaluation by Doppler, the method has some limitations. Doppler methods depend on the insonation angle and require experienced physicians. NT-proBNP values correlate to morphofunctional behavior and echocardiographic variables changes after surgical treatment of AOS, and decreased levels of this biomarker can be observed on the postoperative period. The results of the study by Nagueh et al[11] support this statement. This behavior can be explained by a reduction of blood flow resistance and LV hypertrophy after surgery, leading to a reduction in LV mass and diastolic wall tension, consequently reducing natriuretic peptide release. The peptides, though, do not return to normal levels due to the aortic-LV pressure gradient generated by the aortic valve prosthesis[11].

In a postoperative study, Frederiksen et al[25] showed a good correlation between E/E' echocardiographic ratio and NT-proBNP levels, something that was not seen for the E/A ratio. The prognostic importance and predictive ability for cardiovascular events of natriuretic peptides such as NT-proBNP have been recently considered a study subject on the medical literature. Berger-Klein et al[12] had already studied NT-proBNP in the postoperative evolution of symptomatic AOS patients and observed its predictive effect, independent from survival. Besides, Gerber et al[26] suggested an predictive effect of symptoms development in AOS patients.

The present study showed a correlation between the different echocardiographic variables that characterize diastolic dysfunction[27] and NT-proBNP serum levels. We were also able to demonstrate that high preoperative NT-proBNP levels predict greater LV mass regression after surgical treatment, in spite of the indexed LV mass values. This fact suggests that NT-proBNP measurement may be good prognostic marker in AOS patients. Also, diastolic function echocardiographic changes in AOS patients precede LV mass increase. When these changes indicate

Table 1 - Echocardiographic variables measured before and after surgery in patients with aortic stenosis

Variable	Time point	Mean	Median	p
LVEF	Before surgery	0.597±0.059	0.59	1.0000
	After surgery	0.609±0.068	0.58	
E/A	Before surgery	0.945±0.531	0.84	0.4181
	After surgery	1.112±0.634	0.83	
IVRT	Before surgery	114.387±14.933	111	0.0072
	After surgery	102.942±17.392	100	
DT	Before surgery	163.258±37.841	160	0.3214
	After surgery	149.896±34.363	165	
E/E’	Before surgery	12.141±4.664	11.1940	0.0379
	After surgery	9.864±3.214	9.3163	
S/D	Before surgery	1.224±0.408	1.20	0.2454
	After surgery	1.125±0.497	1.03	
Mitral A time - Pulmonary A time	Before surgery	27.409±32.131	26	0.0176
	After surgery	9.933±30.357	12.50	
Mitral A velocity - Pulmonary A velocity	Before surgery	72.023± 24.027	71.20	0.9482
	After surgery	70.860± 29.987	71.35	
Mitral A velocity	Before surgery	102.806±25.385	105	0.8437
	After surgery	100.442±27.481	99.80	
Vol. Sist. LA	Before surgery	34.291± 16.666	31	0.0242
	After surgery	25.871± 11.772	23	
Indexed LA Sist. Vol.	Before surgery	19.979±8.646	18.0687	0.0237
	After surgery	15.099±6.637	13.1879	
LA Diast. Vol.	Before surgery	65.548± 29.089	55	0.1115
	After surgery	52.806± 21.233	46	
LAEF	Before surgery	0.451±0.103	0.46	0.0339
	After surgery	0.508±0.108	0.53	
S wave	Before surgery	55.063± 13.113	57	0.8054
	After surgery	54.058±14.401	53.20	
LVDD	Before surgery	53.161±0.914	5.20	0.0002
	After surgery	47.774±0.335	4.80	
LVSD	Before surgery	33.484±0.409	3.30	0.0085
	After surgery	31.194±0.288	3.10	
ESV	Before surgery	44.197±19.956	40	0.1013
	After surgery	38.553± 18.629	35	
EDV	Before surgery	108.777± 47.554	102	0.0194
	After surgery	90.163±41.521	82.25	
Indexed LV mass	Before surgery	219.985± 99.423	188.46	< 0.0001
	After surgery	138.779± 20.409	134.25	
Volume/mass	Before surgery	0.309±0.127	0.3007	< 0.0001
	After surgery	0.466±0.234	0.4360	

LVEF: left ventricle ejection fraction (Simpson method), E/A ratio: E wave/A wave ratio (cm/s), IVRT: isovolumetric relaxation time (ms), DT: deceleration time (ms), E/E’ ratio: E wave/E wave on tissue Doppler of the lateral wall (cm/s), S/D: systolic/diastolic component (cm/s), Mitral A velocity (ms), LA Sist. Vol.: left atrial systolic volume (ml), Indexed LA Sist. Vol.: left atrial systolic volume indexed by body surface area (ml/m²), LA Diast. Vol.: left atrial diastolic volume (ml), LAEF: left atrial ejection fraction (Simpson), S wave: systolic wave (cm/s), LVDD: left ventricle diastolic diameter (mm), LVSD: left ventricle systolic diameter (mm), ESV: end-systolic volume (ml), EDV: end-diastolic volume (ml), Indexed LV mass: left ventricle mass divided by body surface area (g/m²).

Table 2 - Diastolic dysfunction classification (Grades 1 to III, based on E/A, DT, E/E', LA systolic volume parameters), comparing pre- and postoperative time points in patients with aortic stenosis

	GRADE I	GRADE II	GRADE III
	E/A < 1 cm/s	E/A = 1 to 1.5 cm/s	E/A > 2 cm/s
	DT > 240 ms	DT = 160 to 240 ms	DT < 160 ms
	LA systolic volume = 25-30 ml/m^2	LA systolic volume > 30-45 ml/m^2	LA systolic volume > 30-45 ml/m^2
	E/E´ < 8 cm/s	E/E´ 8-15 cm/s	E/E´ > 15cm/s
Before (n)	7 (22.5%)	14 (45.1%)	10 (32.4%)
After (n)	8 (25.8%)	16 (51.6%)	07 (22.6%)
			χ2=0.437, p=0.804

DT: deceleration time, E/A ratio: E wave/A wave ratio, LA: left atrium, E/E': protodiastolic left ventricle filling velocity (E wave, pulsed Doppler)/protodiastolic left ventricle filling velocity (E' wave, tissue Doppler) ratio.

Table 3 - NT-proBNP values measured before and after surgery in patients with aortic stenosis (AOS)

Timepoint	Disease	Mean±SD	Minimum	Maximum	p
Before surgery	AOS	745.37±SD	17	5536	0.001
After surgery		331.85±SD	49.71	1623	

Table 4 - Mean logNT-proBNP values versus diastolic dysfunction level

	NT-ProBNP	p (ANOVA)	p (Bonferroni)
Grade I	4.58	0.027	0.025
Grade II	4.69		
Grade III	4.70		0.080

Table 5 - Spearman and Pearson linear correlations between log-NT-proBNP and echocardiographic variables in patients with aortic stenosis

Variable	Pearson Correlation		Spearman Correlation	
	Correlation	p	Correlation	p
IVRT	0.1787	0.0768	0.164	0.1049
Mitral A time - Pulmonary A time	-0.0570	0.5771	-0.0190	0.8512
E/E'	0.3322	0.0007	0.2953	0.0027
LAEF	-0.3250	0.0013	-0.3120	0.0020
LA Sist. Vol.	0.3054	0.0025	0.3662	0.0002
Indexed LA Sist. Vol.	0.3419	0.0009	0.4253	< 0.0001
LVDD	0.1194	0.2579	0.1307	0.1860
LVSD	0.2052	0.0367	0.2178	0.0264
ESV	0.1383	0.1636	0.1305	0.1888
EDV	0.0706	0.4785	0.0130	0.8960
Indexed LV mass	0.2475	0.0117	0.3126	0.0014
Volume/Mass	-0.2370	0.0161	-0.2730	0.0053

IVRT: isovolumetric relaxation time (ms), Pulmonary A time (ms), E/E' ratio: E wave/E wave on tissue Doppler of the lateral wall (cm/s), LAEF: left atrial ejection fraction (Simpson), LA Sist. Vol.: left atrial systolic volume (ml), Indexed LA Sist. Vol.: left atrial systolic volume indexed by body surface area (ml/m²), LVDD; left ventricle diastolic diameter (mm), LVSD: left ventricle systolic diameter (mm), ESV: end-systolic volume (ml), DSV: end-diastolic volume (ml), Indexed LV mass: left ventricle mass divided by body surface area (g/m²).

Table 6 - Logistic Regression Model for Diastolic Dysfunction Risk

Coefficient	Estimate	Risk	Standard deviation	p
Intercept (basal)	2.4441	-	0.4215	< 0.0001
Log-NT-proBNP (4.78)	0.9714	2.6416	0.3994	0.0150

Log-NTproBNP: logarithm of the brain natriuretic peptide.

moderate to severe LV dysfunction, they are considered an independent factor for late mortality after valve replacement surgery.

Vasan et al[28] proposed a criterion for diagnosing diastolic HF that includes signs and symptoms of HF, preserved LVEF and evidences of diastolic dysfunction (BNP measurement and echocardiographic changes). This, high BNP values can help in the diagnosis of diastolic heart failure in patients with normal systolic function echocardiographic parameters and abnormal diastolic function.

Conclusions

There was an improvement of diastolic function and reduction of LV mass in AOS patients submitted to valve replacement surgery. Besides that, negative LA remodeling and LAEF improvement in the postoperative period were observed compared to pre-procedure values. NT-proBNP values showed a positive correlation with the various degrees of diastolic dysfunction, both pre- and postoperatively.

Author contributions

Conception and design of the research: Boer BPN, Vieira MLC, Grinberg M; Acquisition of data: Boer BPN, Vieira MLC, Abensur H; Analysis and interpretation of the data: Boer BPN, Vieira MLC, Sampaio RO, Abensur H, Oliveira AG, Grinberg M; Statistical analysis and Obtaining funding: Boer BPN; Writing of the manuscript: Boer BPN, Vieira MLC, Sampaio RO, Abensur H, Oliveira AG, Fernandes JR, Grinberg M; Critical revision of the manuscript for intellectual content: Boer BPN, Sampaio RO, Oliveira AG, Fernandes JR, Grinberg M.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by FAPESP.

Study Association

This article is part of the thesis of doctoral submitted by Berta Paula Napchan Boer, from Instituto do Coração - HCFMUSP.

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