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Masterthesis / Original study

Relationships between cardiac biomarkers and heart function in aortic stenosis patients scheduled for surgical aortic valve replacement

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Abstract

Objective: **To investigate whether the plasma levels of four biomarkers can help predict systolic dysfunction of either ventricle and left ventricular diastolic dysfunction in patients suffering severe aortic stenosis and scheduled for aortic valve replacement.**
Background: **There has recently been an increasing interest for the use of biomarkers in the diagnosis, prognostication, and follow-up of heart diseases. Apart from the N-terminal pro B-type natriuretic peptide (NT-proBNP), the relationships between these biomarkers and the different aspects of heart function remain poorly investigated in patients eligible for cardiac surgery. It is plausible that some biomarkers more specifically reflect the dysfunction of one or the other ventricle, or diastolic dysfunction.**
Methods: **This unspecified and therefore exploratory analysis of a previously published prospective observational trial adheres to the applicable EQUATOR guidelines. After Ethics Committee approval and written informed consent, the plasma levels of NT-proBNP, soluble isoform of suppression of tumorigenicity 2 (sST2), Galectin 3, and growth differentiation factor (GDF-15) were measured in an arterial blood sample drawn before induction of anesthesia in 179 patients undergoing aortic valve replacement for aortic stenosis. The monotonic interactions between the biomarkers and various echocardiographic measurements performed during the pre-cardiopulmonary bypass transesophageal echo exam were investigated using the Spearmann correlation coefficient. Whenever a significant correlation was observed, the ability of the biomarker to predict abnormal heart function was investigated using the area under the receiver operating curve (AUROC).**
Results: **Significant correlations were observed between the level of NT-proBNP and the ejection fraction of the left ventricle (LVEF) (ρ=-0.31, P<0.001), or its global longitudinal strain (GLS) (ρ=-0.40, P<0.001). The NT-proBNP was also correlated with the left atrial (LA) volume (ρ=0.23, P=0.03) and the LA reservoir strain (ρ=-0.33, P<0.001). The correlations between the e/e' ratio and both the NT-proBNP (ρ=0.38, P<0.001) and the GDF-15 (ρ=0.24, P=0.006) were significant. No correlation was observed between Galectin 3 and sST2 and any of the echo parameters. The ability of NT-proBNP to predict an LVEF < 50% (AUROC=0.66) and a GLS > -20% (AUROC=0.63) was weak. The ability of NT-proBNP to predict an e/e' ratio > 14 was moderate (AUROC=0.71) and not significantly improved by the addition of GDF-15 (AUROC=0.69, P=0.44)**
Conclusions: **The NT-proBNP had a weak to moderate ability to predict both systolic and diastolic dysfunction of the left ventricle in our patient population. Apart from a weak relationship between GDF-15 and diastolic dysfunction, no significant relationship was observed between any of the other markers tested and the echocardiographic measurements in our patient population.**

Keywords: **Aortic valve stenosis, biomarkers, ultrasonography, correlation of data.**

Prior Presentations: BeSARPP Graduation Day 2024.
Internal Review Board approval and written informed consent were obtained. This study was approved by the local ethical committee (Comité d'éhtique hospitalofacultaire de Liege, Chairperson Pr. V. Seutin; Ref 2015/309) and registered with clinicaltrial.gov (NCT02641665).
Patients were included during the period between January 2016 and December 2017.

Introduction

Cardiovascular diseases, continue to pose significant challenges to global healthcare systems. (ref) In recent years, there has been a growing interest in identifying reliable biomarkers that can assist in the screening, diagnosis, prognostication, and follow-up of patients suffering heart diseases[1]. The national institute of health defines biomarkers as any substance that is objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or pharmacological responses to therapeutic interventions[2]. The natriuretic peptides, including the most popular N-terminal pro B-type natriuretic peptide (NT-proBNP), are markers of myocardial stretch and mechanical stress. Among heart failure biomarkers, they have been by far the most widely studied, and their clinical utility has been confirmed across a wide range of heart diseases[3]. Accordingly, both the European Society of Cardiology and the American Heart Assocation recommend measuring the natriuretic peptites for the diagnosis of heart failure[4]. Although natriuretic peptides are the only heart failure biomarkers routinely used in clinical practice, many other candidates are currently being investigated. They can be classified according to the pathophysiological process to which they are mainly related. These processes include neurohumoral activation, myocardial injury, myocardial inflammation, platelet activation, myocardial remodeling and stress, or lipid metabolism disturbances. The picture is further complicated by the fact that some degree of overlap exists between these biological processes[5]. Among all these potentially new markers, Galectin 3, the soluble isoform of suppression of tumorigenicity 2 (sST2) and the growth differentiation factor-15 (GDF-15) have already proven useful for the prognostic stratification of adult patients undergoing heart valve surgery[6,7].

Galectin 3 and sST2 are both markers of extracellular matrix remodelling. Briefly, Galectin-3 is a β-galactoside lectin binding protein secreted by macrophages, possibly in response to aldosterone. Its stimulates fibroblasts and collagen production which causes myocardial fibrosis and remodeling[8]. The soluble isoform of suppression of tumorigenicity 2 is member of the interleukin (IL-1) receptor family. Since it lacks both the transmembrane and intracellular domains, it acts as a decoy receptor for interleukin 33 (IL-33). As a results it prevents IL-33 to bind the ST2 and exerts its protective action against hypertrophy and fibrosis[9]. The GDF-15 is a growth factor which belongs to the superfamily of the transforming growth factor-β. GDF-15 is generally thought to exert protection against apoptosis, hypertrophy and adverse remodeling. However, after a myocardial infarction, higher levels of GDF-15 predict heart failure and death. Similarly, high levels of GDF-15 have been observed in patients suffering heart failure with preserved ejection fraction (HFpEF) and diastolic dysfunction[10].

As mentionned above, these markers reflect different aspects of cardiac stress and remodeling. In addition to their prognostic significance, it is therefore not impossible that some of them may be more specific of a particular type of myocradial dysfunction[11]. The primary aim of the present stutdy was to investigate the relationships between NT-proBNP, Galectin 3, GDF-15, and sST2, and the systolic function of either ventricles as well as left ventricular diastolic function in patients undergoing heart aortic valve replacement for aortic stenosis. The secondary objetive was to evaltuate whether some of these biomarkers had the ability to predict one of these aspects of myocardial dysfunction more specifically.

Methods

Study design and participants

This study consists in an unspecified and therefore exploratory analysis of a previously published prospective observational trial[7]. The original protocol was approved by our local ethics committee (Comité d'éhtique hospitalo-facultaire de Liege, Chairperson Pr. V. Seutin; Ref 2015/309) and registered with clinicaltrial.gov (NCT02641665) and all patients gave informed consent. The manuscript adheres to the applicable Enhance the QUality and Transparency Of health Research (EQUATOR) guidelines.

Eligible patients were adults suffering aortic stenosis and who underwent an elective single aortic valve replacement with or without associated coronary artery bypass grafts at the Centre Hospitalier Universtiraire de Liège between January 2016 and December 2017. Exclusion criteria were, inability to consent, a history of previous cardiac surgery, a preoperative estimated glomerular filtration rate $\leq$ 30 ml·min-1, active endocarditis, atrial fibrillation, liver cirrhosis, and an implanted permanent pacemaker.

Outcome measures and variables

The baseline characteristics of the patients and the operative data were retrieved from the institutional electronic medical record.

Echocardiographic measurements

A comprehensive transesophageal echocardiographic examination was performed in all patients after induction of general anesthesia and before the initiation of cardiopulmonary bypass. Studies were transferred to a dedicated workstation for offline analysis (Qlab version 10.5 Software, Philips Medical, Belgium). The end-diastolic and end-systolic volumes of the left ventricle (LV) were estimated using the biplane modified Simpson's method. A 4-beat full 3D volume was also acquired in to obtain a measurement of left ventricular volumes and ejection fraction. Mitral inflow velocities and tissue Doppler velocities of the lateral portion of the mitral valve annulus were obtained from the mid-esophageal 4-chamber view. Two-dimensional speckle tracking with Automated Cardiac Motion Quantification (Qlab version 10.5 Software, Philips Medical, Belgium) was used to calculate longitudinal strains. The integrity of the tracking was visually checked and adjusted whenever deemed necessary. The R wave of the EKG and the time to aortic valve closure were used to identify the end of diastole and the end of systole, respectively. The peak systolic longitudinal strain of the LV (GLS) was obtained for the three mid-esophageal views of the left ventricle. The QLAB Automated Cardiac Motion Quantification LV strain software was also used to measure both the peak systolic global longitudinal and free wall longitudinal strain of the right ventricle as well as the peak systolic left atrial strain. Finally, the fractional area change of the right ventricle was obtained from the mid-esophageal 4-chamber view.

Biomarkers analyses

An arterial blood sample was drawn in the operating room after insertion of the arterial line and before anesthesia induction. Blood samples were centrifuged for 10 minutes (3500 RPM). Since it was not possible to carry out the analyses on the same day, plasma and serum were frozen at −80◦C for later analysis excepted for NT-proBNP. The Cobas 8000 (Roche Diagnostic, Manheim, Germany) was used to measure by immunoassay NT-proBNP(Normal Values (NV):< 103 ng·L-1 men <50 years old, Limit of Detection (LOD)=5 ng·L-1). For Galectin-3 measurement, we used an enzyme-linked fluorescent assay (Biomerieux, France) (NV:<17.9 ng·mL-1,LOD:2.4ng·ml-1). Soluble ST2 was measured using a high sensitivity sandwich monoclonal immunoassay (Presage® ST2 Assay, Critical Diagnostics, San Diego, California)(NV:<35 ng·ml-1, LOD 1.31ng·ml-1). GDF-15 was determined by quantitative sandwich enzyme immunoassay technique (R&D System, Minneapolis)(NV: 337-1060 pg·mL-1, LOD= 2pg·mL-1).

Statistical Analyses

The distribution of continuous variables was assessed using histograms and the Shapiro-Wilk test. These are summarized as mean±sd or median [p25-p75] as appropriate. Dichotomous variables are presented as count (percent).

The relationships between the preoperative plasma level of each of the four biomarkers and the echocardiographic measurements was investigated visually using two-way scatter plots. The monotonic interactions between the biomarkers and the echo measurements were then quantified using the Spearman correlation coefficient.

Whenever a significant interaction was identified between a biomarker and an echocardiographic measurement, the predictive ability of this particular biomarker for an abnormal value of the corresponding echo measurement was assessed using the area under the receiver operating characteristic curve (AUROC).

No formal sample size estimation was performed a priori. This original work was supported by a grant from the "Conseil Médical du CHU de Liege" that allowed us to measure the four plasma biomarkers in a total of 250 patients of whom 179 underwent aortic valve replacement.

Given the fact that a total of 28 correlations were investigated between the four biomarkers and the echocardiographic measurements, a P value < 0.001 was considered statistically significant for these analyses. For the other analyses, a usual P value of 0.05 was considered as the threshold of statistical significance.

Statistical analyses were performed using Stata 15.0 (StataCorp LP, College Station, TX).

Results

A total of 250 patients were included in original study of whom 179 underwent aortic valve replacement and were included in this secondary analysis (Figure 1). Baseline characteristics and operative data of these patients are all summarized in Table I. The echocardiographic measurements and preoperative plasma level of the four biomarkers are presented in Table II. Unfortunately, some echo measurements could not be performed in all patient. In particular, the full 3D volume could only be exploited in 92 patients. As a result, the 3D data were not considered for further analyses.

The correlations between the four biomarkers and the electrocardiographic measurements are

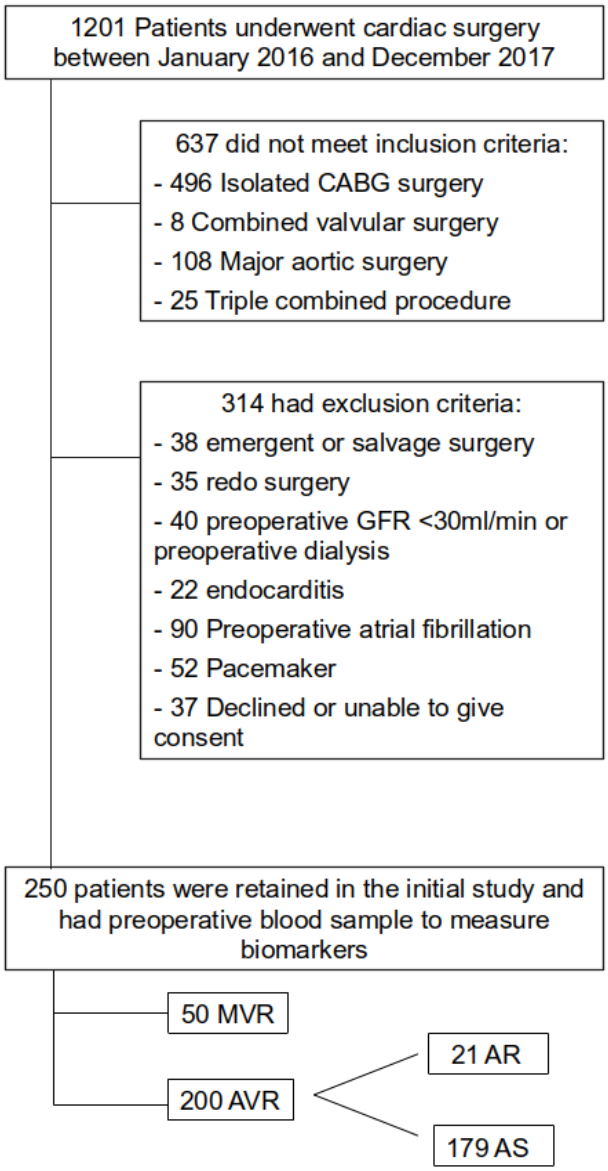

Fig. 1 — Flow Chart of the Study. CABG, Coronary Artery Bypass Grafting. GFR, Glomerular Filtration Rate. MVR, Mitral Valve Replacement or Repair. AVR, Aortic Valve Replacement. AR, Aortic Regurgitation. AS, Aortic Stenosis.

summarized in Table III. The NT-ProBNP was significantly correlated with the left ventricular ejection fraction (LVEF) and the GLS, two measures of the systolic function of the left ventricle. None of the other three biomarkers was found to be correlated with the systolic LV function. No significant correlation was observed between any of the biomarkers and the measurements of the RV systolic function. The NT-ProBNP was significantly correlated with the lateral e/e' ratio and the reservoir strain of the LA, two measures of LV diastolic function. Again, no significant correlation was found between the other biomarkers and the measures of LV diastolic function.

The ability of the NT-proBNP to predict abnormal systolic left ventricular function was weak to moderate. Indeed, the area under the receiver operating curve was 0.66 (95% confidence interval (CI): 0.56-0.75) for a LVEF < 50 % and 0.63 (95%CI: 0.54-0.71) for a GLS > 20% in absolute value (Figure 2a). The NT-proBNP also a good predictive ability for abnormal LV diastolic function. The AUROC was 0.71 (95%CI: 0.61-0.81) for an e/e' ratio > 14 (Figure 2b).

Discussion

The main finding of this study is that, among the four biomarkers tested, only the NT-proBNP was significantly correlated to the echo measurements of both systolic and diastolic function of the LV. Furthermore, the preoperative plasma level of NT-proBNP had a weak to moderate ability to predict abnormal systolic LV function and an good ability to predict abnormal LV diastolic function. None of

Table I. — Patients and Procedure Characteristics.

	All Patients (n=179)
Age(y)	73 [67-80]
Female gender, n(%)	61 (34.1)
BMI(kg.m²)	27.3[24.2-30.8]
LVEF	
> 50 %	147 (82.1)
31-50%	29 (16.2)
21-30%	3 (1.7)
< 20 %	0 (0)
HTN (%)	138 (77.9)
NYHA III- IV, n(%)	58 (32.4)
Insulin dependent diabetes	12 (6.7)
Creatinine (mg/L)	10.5 [8.5 -12.5]
Combined procedure, n (%)	62 (33.6)
COPD (%)	18 (10.1)
Systolic pulmonary arterial blood pressure > 55mmHg, n(%)	6 (3.3)
Extracardiac arteriopathy, n(%)	29 (16.2)
Urgent surgery (%)	10 (5.6)
EuroSCORE II, %	2.2 [1.3-3.9]
CPB (min)	87 [71-112]
NTproBNP (pg/mL)	556 [250-1356]
sST2 (ng/mL)	24.2 [19.0-33.2]
Galectin3 (ng/mL)	15.7 [12.4-19.4]
GDF15 (pg/mL)	1260 [922-1761]

Data are presented as median [p25-p75], mean(sd) ,or n(%). y, year ; BMI, Body Mass Index ; LVEF, Left Ventricular Ejection Fraction ; HTN, Hypertension ; NYHA, New York Heart Association functional class ; AVR, Aortic Valve Replacement ; MVR, Mitral Valve Replacement ; COPD, Chronic Obstructive Pulmonary Disease ; CPB, Cardiopulmonary Bypass duration; sST2, soluble form of suppression of tumorigenicity; GDF 15, Growth differentiation factor-15.

Table II. — Patients and Procedure Characteristics.

Preoperative plasma levels of biomarkers		
		n
NTproBNP (pg/mL)	556 [250-1356]	179
sST2 (ng/mL)	24.2 [19.0-33.2]	
Galectin3 (ng/mL)	15.7 [12.4-19.4]	
GDF15 (pg/mL)	1260 [922-1761]	
Echocardiographic measurements		
LV EDV (mL)	62.3 [45.3-83.3]	170
LV ESV (mL)	24.5 [15.9-38.3]	
LVEF (%)	57.3[47.6-66.8]	
3D LV EDV (mL)	78.6[57.6-110.0]	92
3D LV ESV (mL)	36.2 [21.0-53.0]	
3D LVEF	53.7 [42.1-67.0]	
LV GLS (%)	-18.7 [-21.0 - -15.6]	136
RV Strain (%)	-22.7 [-27.1 - -18.9]	123
RV free wall strain (%)	-23.5 [-27.8 - -19.3]	123
RV FAC (%)	45.6 [39.1 – 54.5]	159
e/e’	10.6 [7.4 – 14.3]	132
LA volume (mL)	50.5 [33.1-66.9]	160
LA reservoir strain (%)	18.8 [12.6 – 23.0]	128

Data are presented as median [p25-p75], mean(sd) ,or n(%). sST2, soluble form of suppression of tumorigenicity; GDF 15, Growth differentiation factor-15. LV, Left Ventricle. EDV, end-diastolic volume. ESV, end-systolic volume. LVEF, left ventricular ejection fraction. GLS, global longitudinal strain. RV, right, ventricle. FAC, fractional area change. LA, left atrium.

Table III. — Correlations between preoperative plasma levels of biomarkers and echocardiographic measurements.

	NT-proBNP		GDF-15		Galectin 3		sST2	
	ρ	P	ρ	P	ρ	P	ρ	P
LV Systolic Function								
$LVEF_{mbs}$	-0.31	<0.001	-0.12	0.12	0.08	0.29	-0.06	0.45
GLS	0.4	<0.001	0.10	0.21	-0.02	0.79	0.16	0.07
RV Systolic Function								
FAC	-0.02	0.83	-0.09	0.26	0.10	0.19	0.02	0.77
RV Strain	0.18	0.05	0.2	0.03	0.14	0.10	0.14	0.17
Left Atrial Function and Volume								
LA Volume	0.23	0.03	0.04	0.6	0.05	0.55	-0.00	0.98
E/e' lat.	0.38	<0.001	0.24	0.006	0.18	0.04	-0.12	0.16
Systolic LA strain	-0.33	<0.001	-0.11	0.23	-0.12	0.17	-0.06	0.47

LVEFmbs, left ventricular ejection fraction by modified biplane Simpson's method. GLS, global longitudinal strain of the left ventricle. FAC, fractional area change. RV, right ventricle. LA, left atrium.

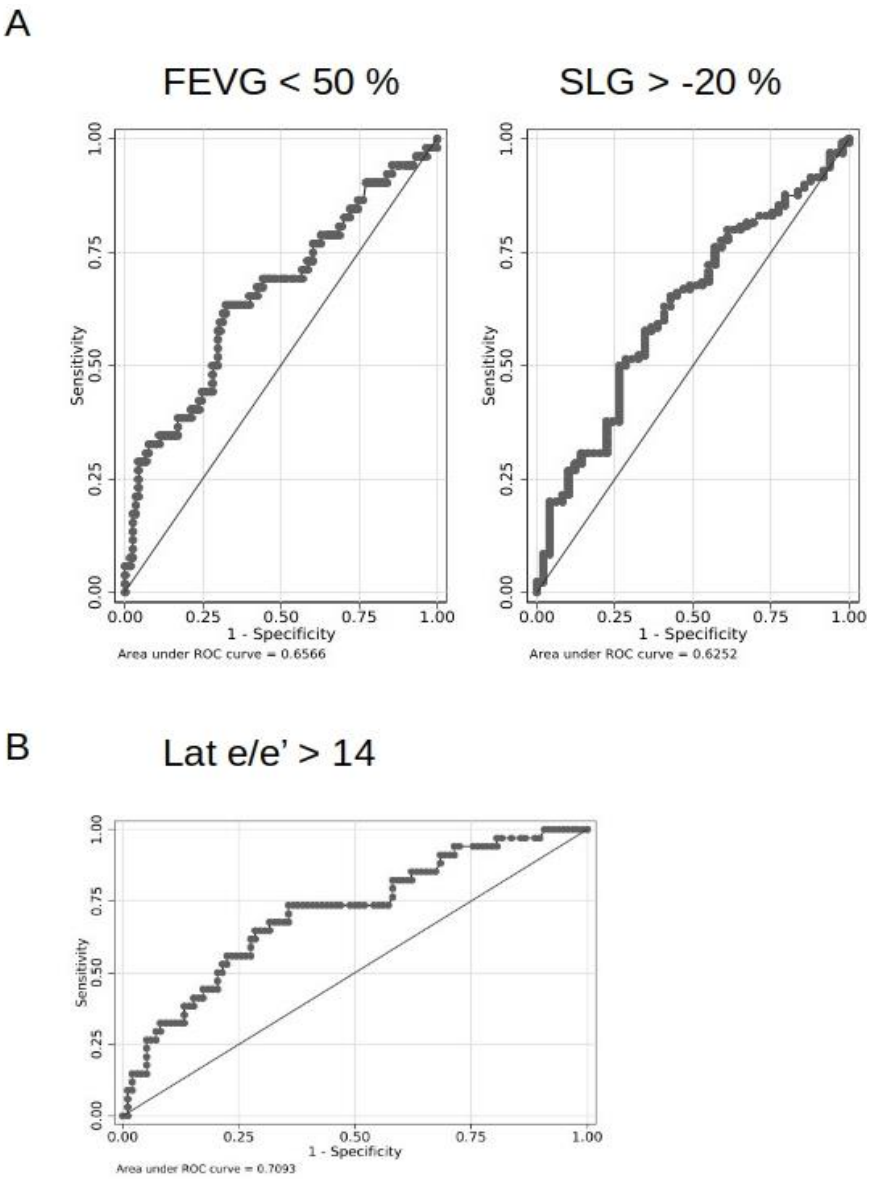

Fig. 2 — A. Receiver Operating Characteristic Curves for prediction of an abnormal systolic LV function based on the preoperative level of NT-proBNP. B. Receiver Operating Characteristic Curves for prediction of a lateral e/e' ratio > 14 based on the preoperative level of NT-proBNP. LVEF, left ventricular ejection fraction. GLS, peak systolic global longitudinal strain.

the biomarkers was significantly associated with RV systolic function.

The correlation between the NT-proBNP plasma level and several measurements of systolic and diastolic function of the left ventricle has long been reported and in this regards, our results are largely consisted with those of previously published studies[12].

Regarding the plasma level of Galectin-3, our results are consistent with those of a previous study where no significant correlation could be observed between the plasma level of Galectin-3 and several echocardiographic measures including the LVEF in a group of symptomatic patients suffering from severe aortic stenosis[13]. Nevertheless, in contrast with our results, Bobrowska et al. observed no correlation between the NT-proBNP and the LVEF. There was however a trend towards higher NT-proBNP levels in patients with decreased LVEF and their study might have lacked statistical power with only 80 patients included.

The findings of this study diverge from several prior investigations that have demonstrated a correlation between plasma levels of sST2 and various indicators of diastolic dysfunction, such as left atrial volume, and the e/e' ratio[14,15]. One potential explanation for these discrepancies is that the echocardiographic measurements were conducted via transesophageal echocardiography (TEE) in our study, as opposed to transthoracic echocardiography used in the other studies. The agreement between the two imaging modalities for these measurements has been reported to be poor[16,17]. It is also not impossible that anesthesia and positive pressure ventilation induce acute changes in diastolic function and alter the relationships between the diastolic parameters and the levels of biomarkers. We also found no correlation between sST2 and both the LVEF and the GLS. This contrasts with the results from Fabiani et al. However, they enrolled both healthy individuals and AS patients in their study. Although there is a clear difference between the sST2 plasma level of AS patients and healthy individuals, the existence of a correlation between GLS and sST2 in the AS patients group is less obvious. In addition and despite the fact that they used the same enzyme-linked immunosorbent assay (ELISA) kit as we did, the mean plasma level of sST2 are much higher in their population, which raises the question of comparability[15].

Recently, Gumauskine et al reported a somewhat indirect correlation between the plasma levels of GDF-15 et echocardiographic measures of altered diastolic dysfunction such as the E/e' ratio and the LA volume[18]. We observed a similar trend for the E/e' ration but it did not reach statistical significance after adjustment for multiple comparisons. It is however not impossible that GDF-15 is a more sensitive biomarkers of LV diastolic dysfunction than others.

This study has several limitations. Firstly, we only included patients suffering aortic stenosis and for whom a decision of surgical aortic valve replacement had been made. As a results, they were at an advanced staged of the disease and all had elevated baseline values of plasma biomarkers in comparisons to other studies including controls or even less sick patients. It is therefore possible that, for some markers, the plasma level was beyond the range in which a correlation could be established with the echocardiographic measures of heart function. Secondly, and as mentioned above, the echocardiographic measurements were performed using transesophageal echo while patients were anesthetized and under positive pressure ventilation. It is well established that both the use of transesophageal echo as opposed to transthoracic as well as anesthesia and positive pressure ventilation significantly affect the results of some of the echocardiographic measurements[16,17,19]. The measurements of atrial and ventricular volumes as well as the ejection fraction are however usually considered reliable[20]. Thirdly, for the systolic right ventricular dysfunction, which is a late event in aortic stenosis, the event rate may have been too low and our study underpowered regarding this particular aspect of heart function. Finally, no formal sample size estimation was performed a priori since the study consisted in a secondary analysis of a previous research. A total of 179 patients were included but, admittedly, not all measurements could be obtained in every patient, mainly as a result of insufficient image quality. The peak systolic left atrial strain was the less frequently obtained parameter and could only be measured in 128 patients. This sample size allows the detection of an Spearman correlation coefficient of 0.25 at an alpha level of 0.05 and with a power of 0.8. We therefore believe that the present study is adequately powered to rule out a very weak to weak correlation between the biomarkers and the echocardiographic measurements.

In conclusion, the results of the present study confirm the correlation between the NT-proBNP and both the systolic and diastolic function of the left ventricle. No correlation was observed with the systolic function of the right ventricle. The three newer markers appear to add little value in terms of prediction of systolic or diastolic function of either ventricle in this clinical context.

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plasma concentration of the biomarkers in the studied population.

There is no conflict of interest to be declared.

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