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Original article

Role of cardiovascular biomarkers for the assessment of mitral stenosis and its complications

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ABSTRACT

Background: Mitral stenosis (MS) may cause progressive dyspnea on exertion, pulmonary hypertension (PH), atrial fibrillation and right ventricular (RV) failure. Patients with MS presenting with change in dyspnea severity often require a complete cardiologic assessment, but the use of biomarkers may be an alternative for the initial assessment of MS and its complications. The aim of this study was to evaluate the role of several cardiovascular biomarkers for this purpose.
Methods: Clinically stable patients with moderate or severe MS were included in this prospective multicenter observational study. ECG, transthoracic echocardiography and biomarker measurement (BNP, MR-proANP and sCD146) were performed at inclusion. One cohort of patients with pre-capillary PH (PAH) was included for comparison of biomarker levels in different etiologies of PH.
Results: A total of 117 MS (70% severe, 30% moderate stenosis) were included. Plasma levels of all three biomarkers were higher in severe MS compared to moderate MS. PH was associated with higher levels of BNP and MR-proANP. The presence of atrial fibrillation increased plasma levels of BNP and sCD146, whereas MR-proANP was not affected by atrial fibrillation. PAH patients had higher levels of sCD146 compared to MS patients with PH. RV dysfunction was associated with higher levels of sCD146.
Conclusion: MS and its complications affect plasma levels of cardiovascular biomarkers. The use of MR-proANP may be helpful for the assessment of severe stenosis and the presence of PH in the early phase. sCD146 might help identifying patients with more advanced PH and RV-dysfunction.

1. Introduction

Mitral stenosis (MS) is often a sequel of rheumatic fever and, although rheumatic fever has greatly decreased in industrialized countries, MS still causes significant morbidity and mortality worldwide. MS may not cause symptoms for years and then present with progressive dyspnea on exertion, pulmonary hypertension (PH), atrial fibrillation, right ventricular (RV) failure.

Patients with MS presenting with change in dyspnea severity often require a complete cardiologic assessment including ECG and echocardiography to exclude disease progression or complications. Indeed, echocardiography allows a comprehensive assessment of valve morphology, severity of stenosis and associated conditions. However, as dyspnea is a frequent cause of consultation of emergency departments and echocardiography is not always immediately available, especially in countries where MS is particularly frequent, the use of biomarkers may be an interesting alternative for the initial assessment of MS and its complications.

The aims of this study were to evaluate the role of several cardiovascular biomarkers (BNP, MR-proANP, sCD146) in the assessment of MS severity and its complications, in particular atrial fibrillation, pulmonary hypertension and RV dysfunction. Natriuretic peptides (e.g. BNP, NT-proBNP and MR-proANP) have been shown to accurately identify

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cardiac origin of dyspnea [1–3]. Very recently, the novel endothelial biomarker sCD146, a marker of peripheral congestion, has been shown to have similar diagnostic properties to detect cardiac origin of acute dyspnea [4].

Aim of the study was a more complete understanding of cardiovascular biomarker behavior in presence of MS. We hypothesized that BNP, MR-proANP and sCD146 might be useful for the assessment of MS severity and its complications, in particular pulmonary hypertension.

2. Methods

2.1. Study population

Consecutive, clinically stable patients with moderate (valve area between 1.5 and 2 cm^2) or severe (valve area < 1.5 cm^2) MS were included in the study between January 1st, 2011 and March 31st, 2015. This prospective multicenter observational study was performed at the University Hospital of Besancon (France), Bichat University Hospital in Paris (France), and Cumhuriyet University Hospital of Sivas (Turkey). Exclusion criteria were: age < 18 years; left ventricular ejection fraction <40%; recent acute coronary syndrome or documented coronary disease; combination of MS with severe aortic valve disease or more than mild mitral regurgitation; recent (<1 month) cardiac decompensation. Patients with high heart rate (>110 beats per minute), uncontrolled hypertension (systolic blood pressure > 180 mm Hg), severe anemia (hemoglobin < 9 g/dL) or pregnancy were excluded as well.

One small cohort (n = 16) of patients with pre-capillary PH (PAH) examined at University Hospital of Besancon was included for comparison of biomarker levels in different etiologies of pulmonary hypertension.

2.2. Echocardiographic study

All patients underwent transthoracic echocardiography at inclusion, and measurements were made in accordance with the recommendations of the European Association for Echocardiography [5]. Severity of mitral valve stenosis (MS) was assessed by planimetric evaluation in the parasternal short axis view. MS was considered severe if the valve area was ≤1.5 cm^2 and moderate if the valve area was between 1.5 and 2 cm^2. Extent of mitral regurgitation was estimated by color Doppler according to an integrative approach [6] Left ventricular (LV) systolic function was evaluated by measurement of the LV ejection fraction by the Simpson's biplane method. The left atrial size was assessed by measuring its area from the apical four chamber view or its volume in both the four and two chamber views. The left atrium (LA) was considered to be dilated if area was >20 cm^2, or volume > 60 mL, or diameter > 40 mm. Pulmonary pressures were calculated from maximal tricuspid regurgitation velocity on continuous Doppler in the apical four chamber view, taking into account the size and compliance of the inferior vena cava. A diagnosis of PH was retained for a tricuspid regurgitation velocity > 2.8 m/s, corresponding to systolic pulmonary artery pressure (PAP) >30 mm Hg. Right ventricular (RV) function was assessed by measuring RV fractional area change (RV fac), tricuspid annular plane systolic excursion (TAPSE) and systolic myocardial velocity at the lateral tricuspid annulus (TAPSE S′). RV dysfunction was defined as the alteration of any one of these three criteria (i.e. RV fac < 40%, TAPSE < 18 mm; TAPSE S′ < 12 cm/s).

2.3. Biomarker testing

Samples of venous blood were drawn on the same day as echocardiography was performed. Samples were centrifuged within 10 min in a refrigerated centrifuge, and stored at −80 °C.

BNP was measured using the ARCHITECT i2000 system (Abbott Laboratories, Chicago, IL, USA). MR-proANP was measured using immunoluminometric assay (B.R.A.H.M.S. AG, Hennigsdorf, Germany) and sCD146 using the CY-QUANT ELISA sCD146 kit (Biocytex, Asnieres, France).

2.4. Statistical analysis

Continuous variables are expressed as median (interquartile range), nominal variables as frequency (percentages). Group characteristics were compared with non-parametric tests: Fisher's exact test or the Mann–Whitney U-test for two groups, as appropriate; Chi-square or the Kruskal–Wallis H-test for three groups, as appropriate. For statistically significant differences between the groups, subsequent pairwise comparisons were performed using Dunn's procedure with Bonferroni correction of the p-value for multiple comparisons. Corrected p-values are reported. Correlation analysis was performed using Spearman's correlation coefficient. The diagnostic performance of all three biomarkers was assessed by receiver operating characteristic (ROC) analysis and expressed as area under the curve (AUC). The null hypothesis was rejected with an adjusted two-sided p-value < 0.05. All analyses were performed with the use of IBM SPSS Statistics, Version 21.0. (IBM Corp, Armonk NY, USA).

2.5. Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki and local national laws and was approved by the local Ethical Committee. All patients provided written informed consent. The study is registered with ClinicalTrials.gov under the number NCT01374880.

3. Results

3.1. Study population

A total of 117 patients, predominantly women (n = 96, 72%) with mitral stenosis were included (France n = 51; Turkey n = 66). In 82 patients (70%) the stenosis was classified as severe and moderate in the other 35 patients (30%). The median planimetric area was 1.34 cm^2 (IQR 1.1–1.58 cm^2) and left atria were dilated in the majority of patients (n = 104, 89%) with a median diameter of 49 mm (42–54 mm) and a volume of 101 ml (75–135 ml). Pulmonary hypertension (n = 83, 71%) and atrial fibrillation (n = 49, 42%) were common among MS patients. Supplementary Fig. 1 illustrates the prevalence of severe stenosis, atrial fibrillation, pulmonary hypertension and their combinations in the MS population. Table 1 summarizes the baseline characteristics of the MS patients. Baseline characteristics of patients with severe MS according to geographic region of enrollment are summarized in Supplementary Table 1.

3.2. Impact of severity of MS, pulmonary hypertension and atrial fibrillation on biomarkers.

Patients with severe MS were older (58 years (IQR 49–69 years) vs. 47 years (IQR 40–59 years), p = 0.001) and reported more severe symptoms (NYHA classes III–IV: 39% vs. 3%, p < 0.001) compared to patients with moderate MS. Meanwhile, half of patients were in functional class NYHA II (39 patients (48%) with severe stenosis and 19 patients (54%) with moderate stenosis).

As shown in Fig. 1A, plasma levels of BNP (p = 0.029), MR-proANP (p = 0.027) and sCD146 (p = 0.011) were higher in patients with severe MS compared to moderate MS. The area under the curve (AUC) after ROC analysis to discriminate between severe and moderate MS was between 0.63 and 0.65 for all three biomarkers (Supplementary Table 2). Fig. 1B illustrates that MS patients with systolic pulmonary pressure above 30 mm Hg had higher levels of BNP (p = 0.025) and MR-proANP (p = 0.034) but no change of sCD146 levels compared to patients without PH. Systolic pulmonary artery pressure (sPAP)

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