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ORIGINAL ARTICLE

Elevated Hyaluronan Levels in Patients with Rheumatic Mitral Stenosis and Pulmonary Arterial Thromboembolism

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Introduction The role of hyaluronan (HA) was previously demonstrated in patients with idiopathic pulmonary arterial hypertension (PAH). Mitral stenosis (MS) and pulmonary arterial thromboembolism (PTE) are important health problems that can cause pulmonovascular pathology. Pulmonary arterial hypertension develops especially in untreated patients with severe MS and most of patients with PTE. However, there is no data about HA levels in patients with MS and PTE. In this study, we investigated HA levels in patients with rheumatic MS and PTE.

Method Study population was divided into three groups. MS group consisted of 18 patients with moderate or severe MS. PTE group consisted of 16 patients with PTE. Control group consisted of 15 subjects without cardiac and pulmonary disease. Percutaneous mitral balloon valvuloplasty (PMV) was performed on all patients in MS group. Mitral gradients and systolic pulmonary arterial pressure (sPAP) were measured in all patients. HA levels were measured at baseline and first month after PMV.

Results Mean sPAP±SD (mmHg) was 23±3 in the control group, 44±9 in the MS group and 66±11 in the PTE group ($p<0.001$). Baseline serum HA levels were significantly correlated with $sPAP^{echo}$ ($r=0.332$ $p=0.03$) and $sPAP^{cath}$ ($r=0.559$, $p=0.007$).
Serum HA levels (ng/ml) in MS were significantly higher compared to controls [39±14 vs 24±11; $p=0.01$]. Patients in PTE group had the highest HA levels (61±21; $p<0.001$). Serum HA levels were significantly decreased at the first month after PMV in patients with MS [MS group: 39±14 (ng/ml), after PMV: 31±8; $p=0.03$].

Conclusion This is the first article showing that both MS and PTE can cause increased serum HA levels. HA levels were decreased with PMV procedure in patients with MS.

Keywords Hyaluronan • Rheumatic mitral stenosis • Pulmonary arterial thromboembolism • Pulmonary arterial hypertension • Percutaneous mitral balloon valvuloplasty

Summary

Higher levels of hyaluronan (HA) were found in pulmonary arterial hypertension (PAH). There is no data about HA levels in mitral stenosis (MS) and pulmonary arterial thromboembolism (PTE). HA levels and systolic pulmonary arterial pressure (sPAP) were measured in MS, PTE and control groups. HA levels and sPAP were higher in MS compared to

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controls and highest in PTE group. HA levels were decreased after PMV in MS.

Introduction

Mitral valve function is closely related to left atrial function and pulmonary vasculature. Increased left atrial pressure in patients with mitral stenosis (MS) is transmitted to the pulmonary vasculature and causes pulmonary hypertension (PAH) and pathological changes in vascular bed [1]. Pulmonary vascular lesions and microvascular ruptures have been shown in MS [2]. It has been also demonstrated that extracellular matrix activity is important for cardiac development [3,4] and can be influenced by overload stimulus [5,6]. Pulmonary arterial thromboembolism (PTE) is also an important health problem that can cause pulmonovascular pathology. Pulmonary arterial hypertension develops especially in untreated patients with severe MS and most patients with PTE.

Hyaluronan (HA) is a glycosaminoglycan and the main component of the extracellular matrix. It is present in synovial fluids, the vitreous body, the lungs, the heart and in some other tissues [7,8]. It was clearly shown that HA has a role in wound healing and also in the inflammatory process, cell proliferation and angiogenesis [9,10]. Increased plasma HA levels and accumulation of HA production around pulmonary arteries have been shown in patients with idiopathic pulmonary arterial hypertension [11,12]. Another study also showed that HA levels were significantly higher in the patients with chronic obstructive pulmonary disease compared to healthy controls [13].

It has been shown that HA is elevated in PAH, thus it is possible that these changes in the pulmonary system may affect the production of HA in patients with MS and PTE [11]. However there is no data in the literature about HA production levels in patients with severe MS and PTE.

In the present study, we investigated HA levels in patients with moderate or severe rheumatic MS and PTE. We also evaluated the effect of haemodynamic changes after percutaneous mitral balloon valvuloplasty (PMV) related to HA level in patients with MS.

Methods

Study population: We consecutively enrolled 15 controls and 34 patients according to the following inclusion criteria:

- **MS group:** Moderate or severe rheumatic MS without any pulmonary disease
- **PTE group:** PAH due to pulmonary arterial thromboembolism (PTE)

Eighteen patients with moderate or severe rheumatic MS who were scheduled to undergo a PMV were included in the MS group. PMV was performed on all patients in the MS group. Sixteen patients diagnosed with PAH were included in the PAH group. The control group consisted of 15 healthy subjects without any cardiovascular or pulmonary disease. Patients with any other pulmonary and cardiac disorders such as chronic obstructive pulmonary disease, atrial fibrillation, systolic and diastolic heart failure, inflammatory disease or active inflammation, renal failure (creatinine> 1.3 mg /dl), liver disease, co-morbidity conditions such as morbid obesity, malignity were excluded from the study. Diagnosis of MS was established with clinical evaluation and echocardiographic examination. PAH due to chronic PTE was defined as a systolic pulmonary arterial pressure (sPAP) of greater than 40 mm Hg at rest by echocardiography [14]. The study was approved by the local ethics committee of Erciyes University Medical Faculty. Signed informed consent was obtained from all patients.

Echocardiography: Echocardiographic examination was performed by a trained cardiologist using a Vingmed system V ultrasound device with 3.5 MHz probe. All measurements were performed at baseline in all patients and repeated at the first month in MS group. Following a 5 min resting period M-Mode, 2-dimensional and Doppler echocardiograms were obtained from the subjects in the left lateral decubitus position. Left ventricular and left atrial dimensions were measured in the parasternal long axis view. Left ventricular end diastolic and end systolic dimensions were measured using M mode echocardiography. Left ventricular ejection fraction was obtained by means of the Teichholz equation and Simpson method [15].

Mitral valve area was measured using planimetry and pressure half time methods. Peak and mean mitral transvalvuler peak (PG) and mean gradients (MG) were measured by using Doppler echocardiography according to the guidelines of the American Society of Echocardiography [16]. Moderate MS was defined as decreased mitral valve areas 1.0-1.5 cm^2 and increased MG: 5-10 mmHg. Severe MS was defined as decreased mitral valve areas <1 cm^2 and increased MG>10 mmHg. Pulmonary artery pressure was estimated by continuous wave Doppler echocardiography using the modified Bernoulli equation (4 + [peak tricuspid velocity] with 10 mmHg added for the estimated right atrial pressure [17,18].

Percutaneous mitral balloon valvotomy procedure: Percutaneous mitral balloon valvotomy was performed according to the stepwise Inoue technique as previously described [18,19]. Cardiac catheterisation was performed to measure haemodynamic parameters including sPAP and gradient in mitral valve before and immediately after PMV [20].

Biochemical and haematological measurements: Blood samples were drawn in the morning after a fasting period of 12 hours. The levels of glucose, blood urea nitrogen, creatinine, lipid profile, liver function tests, and uric acid were determined by Thermo Clinical Lab Systems (Thermo Clinical Labsystems, Vantaa, Finland). Haemoglobin, haematocrit, platelets, and white blood cell were determined using a blood counter (Sysmex K-1000, Sysmex Medica Co. Japan).

Measurement of hyaluronan: The levels of HA in the serum were determined by an enzyme linked HA binding assay (Corgenics Inc., Broomfield, CO, USA)[21]. The system uses a capture molecule known as HA binding protein. The