Does the Dıfferent Type of Pulmonary Hypertensıon Cause the Same Effect on Rıght Heart and Serum Asymmetrıcal Dımethylargınıne Levels ın Female Patıents?

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ABSTRACT

Objective: Right heart function is a major determinant of clinical outcome in patients with elevated pulmonary artery pressure due to pulmonary venous hypertension (PVH) and pulmonary arterial hypertension (PAH). Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase. In our study we aimed to evaluate if different type of PH cause the same effect on right heart functions and serum asymmetric dimethylarginine (ADMA) levels in female patients.

Methods: Patients with PAH as group I and patients with PVHT due to mitral stenosis (mitral valve area ≤ 1,5 cm^2, without any additional valve or left heart disease and systolic pulmonary artery pressure ≥ 50 mmHg in transthoracic echocardiography) as group II and healthy control subjects as group III included to the study. Transthorasic echocardiographic evaluations for right heart functions were performed according to the guidelines of the American Society of Echocardiography. Venous blood samples were collected and the serum ADMA concentrations obtained with ELISA kits.

Results: Patients in group I and group II had higher ADMA levels than control subjects. RA area and dimensions, RV volumes, grade of tricuspid regurgitation, systolic PAP, RV wall thickness, RVOT diameters were significantly higher in group I patients than in group II patients. RVMPI was lower and RVFAC, TV systolic tissue doppler velocity were higher in group II patients than in group I.

Conclusion: This study demonstrated that PAH versus PHT caused increased right heart dimensions and impaired right heart functions.

Keywords: Asymmetric dimethylarginine, echocardiography, pulmonary arterial hypertension, pulmonary venous hypertension, RVFAC, TAPSE, Tei index

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INTRODUCTION

Pulmonary hypertension (PHT) is a pathological condition determined as an increase in mean pulmonary arterial pressure (PAP) ≥25 mmHg as assessed by right heart catheterization. Pulmonary arterial hypertension (PAH) is associated with the presence of precapillary PH (1) It is a life-threatening disease group which constitues of eisenmenger syndrome, idiopathic PAH, drugs associated PAH, connective tissue disease, HIV enfection, portal hypertension and characterized by elevated pulmonary artey pressure which leads right ventricular failure and death. In PAH patients the clinical course and pathological findings of pulmonary vascular bed is similar and they have the worst prognosis than the other disease groups.

Pulmonary venous hypertension (PVHT) is a well-characterized cause of pulmonary hypertension in patients with left heart disease. Mitral stenosis is the most common reason of PVHT in this group. The increase of pulmonary artery pressure is associated with the degree of mitral stenosis and structural alteration in the pulmonary vascular system (2-4). Severe PHT may ocur in patients with mitral stenosis and pulmonary artery pressure may be as elevated as seen in PAH patients. (4-13). Endothelial dysfunction and decreased nitric oxide production are suggested pathophysiological mechanisms (14). Persistently increased pulmonary venous pressure may cause pathological changes in the pulmonary veins and arteries, lead to increase of pulmonary vascular resistance. Structural changes in pulmonary vascular endothelium may cause decreased production of nitric oxide (15-18).

Endothelium-derived nitric oxide (NO) is an endogenous vasodilator which is primarily synthesized from L-arginine (19,20). Endothelial dysfunction is associated with decreased production and bioavailability of nitric oxide (NO) (2,4). Asymmetric dimethylarginine ADMA and mono methylarginine (MMA) are endogenous inhibitors of NO synthase (21,22). Higher levels of serum ADMA have been found in patients with IPAH,

systemic sclerosis and pulmonary tromboembolism. These studies demonstrated that ADMA levels were correlated with increased pulmonary vascular resistance and survival (23-26).

The right heart is the target structure in patients with PH. There is no data about the effect of various type of PH on right heart morphology and functions. In our study we aimed to compare the echocardiographic indices of the right heart and serum ADMA levels between patients with PVH and PAH.

METHODS

The study was performed with protocols approved by the Ethics Committee.

Subjects

The subject of our study were selected among female patients aged 18-75 years who were admitted to the Cardiology Clinic between 2011 and 2013. Patients with PAH (due to Eisenmenger syndrome, IPAH, connective tissue disease) as group I and patients with mitral stenosis (mitral valve area $\leq$ 1,5 cm^2, without any additional valve or left heart disease and systolic pulmonary artery pressure $\geq$ 50 mmHg according to transthorasic echocardiographic evaluation) as group II and healthy control subjects without relevant medical problems as group III were included to the study. Right heart catheterization performed to patients during diagnosis. PAH was defined as present if the mean pulmonary arterial pressure was $\geq$25 mmHg, pulmonary capillary pressure was<15 mmHg, and the pulmonary vascular resistance was $\geq$3 (240 dynes/s/cm^{-5}) WU (27).

Patients with PAH and with PH were recieving proper treatment according to guidelines (1, 28) during the study. Detailed history and physical examination including age, gender, and echocardiography findings were recorded.

Patients receiving drugs affecting the ADMA level (L-arginine, ACE inhibitors, metformin, thiazolidinediones, estrogens, vitamin D, folic Acid, fenofibrates) and liver

disease, renal disease, acute coronary syndrome, congestive heart failure, pregnancy, diabetes mellitus, hypertension, smoking, hyperlipidemia, atrial fibrillation were excluded from the study.

Transthorasic echocardiographic evaluation

Transthorasic echocardiographic evaluations were performed by an experienced echocardiographer with the use of a ultrasound system (Vivid 7, Vingmed, GE, Norway). Standard tranthorasic echocardiography was performed with the subjects in the left lateral decubitus position and measurements were performed according to the guidelines of the American Society of Echocardiography (29). Two-dimensional (2D) images were obtained from standard windows (parasternal long axis, apical four- and two-chamber, and long-axis views). The estimated pulmonary systolic arterial systolic pressure was calculated as the sum of the transtricuspid gradient and the estimated right atrial pressure. From the apical four-chamber view, right ventricular inflow, parasternal short axis or subcostal view, continuous-wave Doppler echocardiography was used to assess the peak tricuspid regurgitant velocity (30). Pulsed-wave tissue Doppler myocardial velocities were measured in the apical four-chamber view from the lateral mitral annular site and the right ventricular wall at the level of the tricuspid annulus. Pulsed tissue Doppler imaging (TDI) was characterized by a myocardial systolic wave (S) and two diastolic waves –early diastolic (E_m) and atrial contraction (A_m) (31). RV dimension at base is measured at end-diastole in a right ventricle-apical 4-chamber view. RA dimensions as major and minor were calculated in apical 4-chamber view. RA area was measured at end-systole. Tricuspid regurgitant velocity (TRV) was determined at apical 4-chamber view. In parasternal short-axis view right ventricular outflow tract (RVOT) velocity was measured and then RVOT VTI was calculated. TRV/RVOT VTI >0.2 indicated increased PVR according to Abbas formula (32). The

patients with mitral stenosis was divided into two groups; group I patients with normal or decreased PVR and group II increased PVR. RV fractional area change (RVFAC) was measured as: end-diastolic area (cm^2)-end-systolic area (cm^2) / end-diastolic area in apical-4 chamber view. RVFAC should be higher than in normal patients 35%. RV myocardial performance index (RVMPI) or Tei index is calculated as: isovolumic contraction time (ICT) + isovolumic relaxation time (IRT) / RV ejection time (RVET). Tricuspid annuler plane systolic excursion (TAPSE) is determined as with M-mode cursor aligned through the anterior tricuspid annulus in the apical 4-chamber view and recorded as longitudinal displacement of the annulus toward the apex during systole.

Dimethyl arginine

Venous blood samples were collected and centrifuged. The plasma was stored at -80ºC. Concentration of ADMA was measured in plasma samples by using a commercial enzyme immunoassay ELISA kit in duplicate/triplicate samples according to manufacturer's instructions. The ADMA concentrations obtained and the performance of the ELISA have been found to be consistent with other widely applied methods (23,25).

Statistical Analysis

Statistical analysis was performed using the SPSS USA (version 17.0 program). Definitive statistics were expressed as the mean±standart deviation for normally distributed data and as the number and percentage for categorical variables. Results were evaluated using 95% confidence intervals, and $p<0.05$ was considered statisticallly significant. The compliance of numerical variables to a normal distribution was assessed using the Kolmogorov-Smirnov test. Nonparametric data were compared with Kruskal-Wallis and the Mann-Whitney U test.

RESULTS

The study enrolled 67 individuals, including three groups. Group I individuals consisted of 17 patients (pulmonary arterial HT group- 11 patients with Eisenmenger syndrome [6 with ventricular septal defect, 1 patient with aorticopulmonary window, 3 patients with patent ductus arteriosus, 1 patient with atrioventricular septal defect], 4 patients with IPAH, 2 patients with PAH and connective tissue disease (systemic sclerosis). 31 patients with mitral stenosis enroled to group II (pulmonary venous HT group) and 19 healthy control subjects to group III.

Patients in group I and group II had higher ADMA levels than control subjects. The levels of ADMA were not different between group I and group II patients (Table II).

RA area, RA major and minor dimensions, RVEDV, RVESV, grade of tricspid regurgitation, systolic PAP, RV wall thickness, RVOT proximal and distal diameters were significantly higher in group I patients with PAH than in group II patients with PVHT. TV systol time, TV ejection time were similar between groups. RVMPI was lower and RVFAC, TV systolic tissue doppler velocity were higher in group II patients than in group I.

Group II patients were divided to subgorups a; lower PVR and b; higher PVR in patients with mitral stenosis according to Abbas Formula (Table III). RVMPI, RVFAC, TV systolic tissue doppler velocity, PAP were different between groups. Group IIb patients had higher PAP levels, MPI, right atrium dimension, and lower TV systolic tissue doppler derived systolic wave velocity and lower TAPSE than group IIb patients (Table IV).

RV basal diameter , RV Wall thickness, RVOT diameters, RA area were higher and Tei index, RVFAC were lowere in Grup I patients when compared with group IIb patients.

DISCUSSION

To the best of our knowledge, this is the first study which compared echocardiographic indices of right heart and serum ADMA levels between PVHT and PAH patients. This study demonstrated that patients with PAH had increased RA, RV dimensions, volumes and RV wall thickness than PVHT patients. PAP was higher in PAH patients. RVFAC, TAPSE and RVMPI are important echo indices for right ventricular function. Right ventricle function in PVHT patients was better than PAH patients according to RVFAC, TAPSE and Tei index in our study. Our results showed that ADMA levels were higher in PHT patients than control group, but there was no difference between PAH and PVHT patients. Interestingly, although PAH patients had worse right heart indices and higher PAP, ADMA levels were not different between group I and II patients (33-36). As a subgroup analysis, according to Abbas formula (32), in mitral stenosis group, patients with higher PVR had higher ADMA levels than patients with lower PVR. Although it remains to be determined whether this measurement in PVHT patients reflects the presence of pulmonary hypertension or disease severity. Shao et al demonstrated that patients with systolic heart failure had elevated ADMA levels (19) positively correlated with systolic PAP. Altuntaş et al found that patients with pulmonary thromboembolism had similar ADMA levels independent of the severity of PAP (37). Skoro-Sajer et al showed increased ADMA levels were correlated with the severity of pulmonary vascular disease in patients with CTEPD (38). The variable conclusions of the published studies seem to be related to comparing the ADMA levels in the disease state with healthy controls. Gorenflo et al evaluated ADMA levels in congenital heart disease patients and found that high flow in pulmonary vascular system didn’t cause increase in ADMA levels (39). Sanlı et al demonstrated that patients with CHD-PAH had higher ADMA levels than patients with CHD without PAH (40). Our result is not compatible with the other studies. But our study is different with the following aspects, we compared pulmonary venous

hypertensive patients with pulmonary arterial hypertensive patients. According to our results we may suggest ADMA is associated with the presence of PHT not the disease severity.

PVHT and PAH cause the same result, right heart failure via different pathophysiological mechanisms. Yan et al examinated the pulmonary vascular resistance and compliance in patients with mitral stenosis. It has been demonstrated that PVR significantly increases in patients with rheumatic heart valve disease. In some patients PVR remains above the normal levels after mitral valve operation. Therefore it can be assumed that postoperative PVR may be associated with structural remodelling of pulmonary small arteries (41-43). The walls of pulmonary artery vessels in patients with pulmonary hypertension secondary to rheumatic mitral stenosis may undergo structural remodelling that affects the preoperative pulmonary artery pressure. In patients with severe pulmonary hypertension due to mitral stenosis lower responses to vasodilators is possibly due to structural alteration of the artery walls (41). Persistently elevated pulmonary venous pressure due to mitral stenosis leads alveolar-capillary membran remodelling with collagen deposition (44,45). Then pulmonary vascular resistance increases due to medial hypertrophy and neointimal proliferation in distal pulmonary arteries (46).

In our study we found similar right atrium dimensions and right ventricle volumes between group I and group IIb (mitral stenosis with higher PVR) patients. Although PAP level was significantly different between group I and group IIb patients, similar right heart diameters may give rise to thought that pathophysiological course is more than elevation of PAP.

The present study has some limitations. First of all, our study includes a small number of patients. For accurately evaluation, particularly for subgroup analysis, studies with larger population are warranted. Another limitation in our study is that echocardiography was used to evaluate right heart function instead of right heart catheterization findings or

magnetic resonance imaging evaluation. In our study all patients were recieving proper treatment according to guidelines. (Group I patients endothelin antagonists, iloprost, sildenafil – Group II patients beta blockers and diuretic treatment). Particularly for group I pateints we have no information about ADMA levels and echo findings before treatment. It is an major limitation, but cessation of vasodilator treatment in these patients was not ethical. Therefore we had to evaluate under this circumstance. In literature there is no study which evaluate the effect of vasodilator treatment on right heart functions and ADMA levels in patients with PAH and PVHT. Therefore further studies are warranted to identiy the effect of PAH-spesific treatment on ADMA levels and right heart functions.

From this study it can be concluded that ADMA levels were similar between PVHT and PAH patients, although PAH caused worse right heart functions and elevated PAP. Therefore we can assume that ADMA levels might be associated with the presence of PHT, not with the disease severity.

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TABLE 1. Comparison of Echocardiographic findings and ADMA levels between patient groups

Characteristics	Group I n:17	Group II n:31	Group III n:19	p
Age (year)	30±10,26	47±7,30	34±4,84	< **0.05**
RV basal diameter (cm)	4,1±0,65	3,5±0,41	2,2±0,20	< **0.05**
Tei index	0,52±0,12	0,40±0,15	0,30±0,05	< **0.05**
RVFAC (%)	12,0±2,52	16,50±4,46	35±5	< **0.05**
TAPSE (mm)				< **0.05**
TVtissue Dopp s wave (m/s)	12±2,52	16,5±4,46	26±0,97	0,09
RV Wall thickness (cm)	9,50±2,50	11,0±2,75	17±5	< **0.05**
RVOT prox diameter (cm)	0,95±0,26	0,60±0,11	0,30±0,05	< **0.05**
RVOT dis diameter (cm)	3,55±0,37	2,90±0,47	2,00±0,50	< **0.05**
RA area (cm2)	3,20±0,55	2,70±0,53	19,0±0,7	< **0.05**
RA major dimension (cm)	30,0±7,96	19,0±5,10	10,0±2,5	< **0.05**
RA minor dimension (cm)	5,65±0,93	4,75±0,88	2,7±0,2	< **0.05**
RVEDV	5,0±1,21	4,0±0,77	3,3±1,1	< **0.05**
RVESV	25±5,30	16±4,19	15±2,3	< **0.05**
TV systol time (msn)	19±6,65	9±3,32	10±1,1	0.149
TV ejection time (msn)	408±57	430±29	380±19	0.660
Systolic PAP (mmHg)	278±61	277±18	250±20	< **0.05**
ADMA (µmol/L)	103±18	60±10	22±5	0,983
TR grade	1,4±0,18	1,36±0,15	0,64±0,19	< **0.05**
	I	I:3	I :10	< **0.05**
	II:2	II:23	II :0	
	III:14	III:5	III: 0	
	IV:1	IV	IV :0	
Functional capacity	I:0	I	I 12	
	II 3	II 22	II 7	
	III 13	III 9	III	
	IV 1	IV	IV	

(RVFAC: Right ventricular fractional area change, TV: Tricuspid valve; RV: Right ventricle, RVOT: Right ventricle outflow tract, prox: proximal, dis: distal, RA: Right area, RVEDV: Right ventricle enddiastolic volüme, RVESV: Right ventricle endsystolic volüme, PAP: Pulmoner artery pressure, TR: Tricuspid regurgitation, BSA: Body surface area, TAPSE: Tricuspid annuler plane systolic excursion, TY: Tricuspid regurgitation, BSA: Body surface area, ADMA: asymmetric dimethyl arginine)

Table 2: Treatment in group I patients

Treatment	**n : 17**
Endothelin antagonists	5 (29%)
Iloprost	2 (11%)
Sildenafil	2 (11%)
Endothelin + Iloprost	2 (11%)
Endothelin + Sildenafil + Iloprost	6 (38%)

Table 3: Comparison of echocardiographic findings and ADMA levels between group IIa and IIb patients

Characteristics	**Group IIa n:21**	**Group IIb n: 10**	**p**
Age (year)	44,95±7,95	46,90±5,85	0,451
RV basal diameter (cm)	3,67±0,41	3,44±0,37	0,138
TAPSE (mm)	17,64±3,98	13,7±4,42	< **0.05**
Tei index	0,46±0,07	0,65±0,11	< **0.05**
RVFAC (%)	41±7,59	35,8±9,07	0,134
TV tissue Dopp s wave (m/s)	12±2,52	9,2±2,20	< **0.05**
RV Wall thickness (cm)	0,62±0,12	0,62±0,09	0,078
RVOT prox diameter (cm)	2,90±0,5	2,87±0,43	0,563
RVOT dis diameter (cm)	2,9±0,58	2,55±0,25	0,056
RA area (cm2)	18,47±5,83	20±3,03	0,109
RA majör dimension (cm)	4,42±0,86	5,3±0,60	0,069
RA minör dimension (cm)	3,48±0,84	4,05±0,33	< **0.05**
RVEEDV	16,32±4,26	15,04±4,11	0,896
RVESV	9,73±3,37	8,84±3,29	0,761
TV systol time (msn)	417±13,7	463±22,43	0,121
TV ejection time (msn)	292±15,9	268±12,03	0,450
Systolic PAP (mmHg)	51,62±8,45	55,10±14,08	< **0.05**
Left atrial volüme index	76,4±21,79	77,78±23,35	0,729
ADMA (µmol/L)	1,36±0,15	1,43±0,16	0,250
TR grade	I 3 II 16 III 1 IV	I I I7 III 4 IV	0.06

(TAPSE: Tricuspid annuler plane systolic excursion, TR: Tricuspid regurgitation, ADMA: asymmetric dimethyl arginine, RV: Right ventricle, RVFAC: Right ventricular fractional area change, TV: Tricuspid valve; RVOT: Right ventricle outflow tract, prox: proximal, dis: distal, RA: Right atrium, RVEDV: Right ventricle enddiastolic volüme, RVESV: Right ventricle endsystolic volüme, PAP: Pulmoner artery pressure)

Table 4: Comparison of ECHO indices between group I and IIb patients

Characteristics	**Group I n:**	**Group IIb n: 10**	**p**
Age (year)	30±10,26	46,90±5,85	< 0.05
RV basal diameter (cm)	4,1±0,65	3,44±0,37	< **0.05**
TAPSE (mm)	12±2,52	13,7±4,42	0.53
Tei index	0,52±0,12	0,65±0,11	< **0.05**
RVFAC (%)	12,0±2,52	35,8±9,07	< **0.05**
TV tissue Dopp s wave (m/s)	9,50±2,50	9,2±2,20	0,770
RV Wall thickness (cm)	0,95±0,26	0,62±0,09	< **0.05**
RVOT prox diameter (cm)	3,55±0,37	2,87±0,43	< **0.05**
RVOT dis diameter (cm)	3,20±0,55	2,55±0,25	< **0.05**
RA area (cm2)	30,0±7,96	20±3,03	< **0.05**
RA major dimension (cm)	5,65±0,93	5,3±0,60	0.101
RA minor dimension (cm)	5,0±1,21	4,05±0,33	0,207
RVEEDV	25±5,30	15,04±4,11	0.051
RVESV	19±6,65	8,84±3,29	0.067
TV systol time (msn)	408±57	463±22,43	0.134
TV ejection time (msn)	278±61	268±12,03	0.563
Systolic PAP (mmHg)	103±18	55,10±14,08	< **0.05**
ADMA (µmol/L)	1,4±0,18	1,43±0,16	0,434
TR grade	I 2	I	
	II 14	I I7	
	III 1	III 4	
	IV	IV	

(TAPSE: Tricuspid annuler plane systolic excursion, TR: Tricuspid regurgitation, ADMA: asymmetric dimethyl arginine, RV: Right ventricle, RVFAC: Right ventricular fractional area change, TV: Tricuspid valve; RVOT: Right ventricle outflow tract, prox: proximal, dis: distal, RA: Right atrium, RVEDV: Right ventricle enddiastolic volüme, RVESV: Right ventricle endsystolic volüme, PAP: Pulmoner artery pressure)