ORIGINAL ARTICLE

Do the Different Types of Pulmonary Hypertension Cause the Same Effect on Right Heart and Serum Asymmetrıcal Dimethylarginine Levels in Female Patients?

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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. This study aimed to evaluate if different types of pulmonary hypertension (PH) would cause the same effect on right-heart functions and serum ADMA levels in female patients.*

Methods: *This study included patients with PAH as group I, patients with PVH due to mitral stenosis (mitral valve area ≤ 1.5 cm², 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. 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 were obtained with the ELISA kit (DRG® International Inc., Springfield, NJ, USA).*

Results: *Patients in groups I and II had higher ADMA levels than healthy control subjects. Right-atrium area and dimensions, right-ventricular (RV) volumes, grade of tricuspid regurgitation, systolic pulmonary arterial pressure, RV wall thickness, and RV outflow tract diameters were significantly higher in group I patients than in group II patients. Right-ventricular myocardial performance index was lower, and RV fractional area change and tricuspid valve systolic tissue Doppler velocity were higher in group II patients than in group I patients.*

Conclusion: *This study demonstrated that both PAH and PVH caused increase in right-heart dimensions and impairment in right-heart functions.*

Keywords: Asymmetric dimethylarginine, echocardiography, pulmonary arterial hypertension, pulmonary venous hypertension, right-ventricular fractional area change, Tei index, tricuspid annuler plane systolic excursion

INTRODUCTION

Pulmonary hypertension (PH) is a pathological condition which is 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 consists of Eisenmenger syndrome, idiopathic PAH, drugs-associated PAH, connective tissue disease, HIV infection, and portal hypertension. It is characterized by elevated PAP which leads to right-ventricular (RV) failure and death. In patients with PAH, the clinical course and pathological findings of the pulmonary vascular bed are similar, and they have the worst prognosis than the other disease groups.

Pulmonary venous hypertension (PVH) is a well-characterized cause of PH in patients with left-heart disease. Mitral stenosis is the most common reason of PVH in this

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group. The increase of PAP is associated with the degree of mitral stenosis and structural alteration in the pulmonary vascular system (2–11). Severe PH may occur in patients with mitral stenosis, and PAP may be as elevated as seen in patients with PAH (3–4). Endothelial dysfunction and decreased nitric oxide (NO) production are suggested pathophysiological mechanisms (12–14). Persistently increased pulmonary venous pressure may cause pathological changes in the pulmonary veins and arteries, leading to an increase of pulmonary vascular resistance. Structural changes in pulmonary vascular endothelium may cause a decreased production of NO (15–18).

Endothelium-derived NO is an endogenous vasodilator which is primarily synthesized from L-arginine (13, 14). Endothelial dysfunction is associated with a decreased production and bioavailability of NO (13–16). Asymmetric dimethylarginine (ADMA) and monomethylarginine are endogenous inhibitors of NO synthase (13, 14). Higher levels of serum ADMA have been found in patients with idiopathic pulmonary arterial hypertension (IPAH), systemic sclerosis and pulmonary tromboembolism. These studies demonstrated that ADMA levels were correlated with increased pulmonary vascular resistance and survival (17–20).

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

SUBJECTS AND METHODS

The study was performed with protocols approved by the Ethics Committee of Gazi University Faculty of Medicine. The subjects of our study were selected from the female patients (aged 18–75 years) who were admitted to the Cardiology Clinic of Gazi University Hospital between 2011 and 2013. Patients with PAH (due to the Eisenmenger syndrome, IPAH and connective tissue disease) as group I and patients with mitral stenosis (mitral valve area ≤ 1.5 cm^2, without any additional valve or left-heart disease and systolic PAP ≥ 50 mmHg according to transthorasic echocardiographic evaluation) as group II, and healthy control subjects without relevant medical problems as group III were included in the study. Right-heart catheterization was performed in patients during diagnosis. Pulmonary arterial hypertension was defined as present if the mean PAP was ≥ 25 mmHg, pulmonary capillary pressure was < 15 mmHg, and the pulmonary vascular resistance was ≥ 3 (240 dyn $\cdot$ scm^{-5}) Wu (1,21).

During the study, patients with PAH and PH received proper treatment according to guidelines (1, 21). Detailed history and physical examination (including age, gender and echocardiography findings) were recorded.

Patients receiving drugs that would affect the ADMA level (L-arginine, ACE inhibitors, metformin, thiazolidinediones, estrogens, vitamin D, folic acid, and fenofibrates) those with liver disease, renal disease, acute coronary syndrome, congestive heart failure, pregnancy, diabetes mellitus, hypertension, hyperlipidemia, and atrial fibrillation, and those who smoked were excluded from the study.

Transthorasic echocardiographic evaluation

Transthorasic echocardiographic evaluations were performed by an experienced echocardiographer with the use of an 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 (22–24). 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, RV inflow, parasternal short-axis or subcostal view, continuous-wave Doppler echocardiography was used to assess the peak tricuspid regurgitant velocity (TRV) (30). Pulsed-wave tissue Doppler myocardial velocities were measured in the apical four-chamber view from the lateral mitral annular site and the RV wall at the level of the tricuspid annulus.

Pulsed-tissue Doppler imaging was characterized by a myocardial systolic wave (S) and two diastolic waves early diastolic (E_m) and atrial contraction (A_m) (31). Right-vetricular dimension at base is measured at end diastole in an RV-apical four-chamber view. Right-area dimensions as major and minor were calculated in apical four-chamber view. The RA area was measured at end systole. Tricuspid regurgitant velocity was determined at apical four-chamber view. In the parasternal short-axis view, RV outflow tract (RVOT) velocity was measured, and then RVOT velocity time integral (VTI) was calculated. According to the Abbas formula, TRV/RVOT VTI of > 0.2 indicated an increased PVR (22, 23). The patients with mitral stenosis were divided into two groups: group I patients with a normal or decreased PVR

and group II with an increased PVR. Right-ventricular fractional area change (RVFAC) was measured as

$$\frac{\text{End-diastolic area (cm}^2\text{)} - \text{End-systolic area (cm}^2\text{)}}{\text{End-diastolic area in apical four-chamber view (cm}^2\text{)}}$$

Right-ventricular fractional area change should be > 35% as normal value The RV myocardial performance index (RVMPI) or Tei index is calculated as

$$\frac{\text{ICT} + \text{IRT}}{\text{RVET}},$$

where ICT is isovolumic contraction time, IRT is isovolumic relaxation time and RVET is RV ejection time.

Tricuspid annuler plane systolic excursion (TAPSE) is determined with the M-mode cursor aligned through the anterior tricuspid annulus in the apical four-chamber view and recorded as the longitudinal displacement of the annulus towards the apex during systole.

Dimethyl arginine

Venous blood samples were collected and centrifuged. The plasma was stored at −80ºC. The concentration of ADMA was measured in plasma samples by using a commercial enzyme immunoassay ELISA kit (DRG® International Inc., Springfield, NJ, USA) in duplicate/triplicate samples, according to manufacturer's instructions. Concentrations of ADMA were obtained, and the performance of the ELISA were found to be consistent with other widely applied methods (17, 19).

Statistical analysis

Statistical analysis was performed using the SPSS version 17.0 program (IBM Inc., Chicago, IL, USA). Definitive statistics were expressed as the mean ± standard deviation for normally distributed data, and as the number and percentage of categorical variables. Results were evaluated using 95% confidence intervals, and a *p* value of < 0.05 was considered statistically significant. The compliance of numerical variables to a normal distribution was assessed using the Kolmogorov–Smirnov test. Non-parametric data were compared with the Kruskal–Wallis and the Mann–Whitney *U* tests.

RESULTS

In the study, 67 individuals were enrolled and divided into three groups. Group I (PAH group) consisted of 17 patients: 11 patients with Eisenmenger syndrome (6 with ventricular septal defect, 1 with aorticopulmonary window, 3 with patent ductus arteriosus, and 1 with atrioventricular septal defect), 4 patients with IPAH and 2 patients with PAH and connective tissue disease (systemic sclerosis). Group II consisted of 31 patients with mitral stenosis (PVH group). Group III consisted of 19 healthy control subjects. Patients' characteristics were shown in Table 1.

Table 1: Comparison of echocardiographic findings and asymmetric dimethylarginine levels between patient group I, II and III

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**
TV tissue Doppler 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 (cm^2)	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	I12	
	II3	II22	II7	
	III13	III9	III	
	IV1	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 end-diastolic volume; RVESV = right-ventricle endsystolic volume; 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.

Patients in groups I and II had higher ADMA levels than those in group III. The levels of ADMA were not different between groups I and II patients (Table 2).

Right area, RA major and minor dimensions, right-ventricle endsystolic volume, right-ventricle endsystolic volume, 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 PVH. The TV systol time and TV ejection time were similar between groups I and II. The RVMPI was lower, whereas the RVFAC and TV systolic tissue Doppler velocity were higher in group II patients than those in group I.

According to the Abbas formula, group II patients were divided into subgroups: (a) (lower PVR) and (b) (higher PVR) in patients with mitral stenosis (Table 3). The RVMPI, RVFAC, TV systolic tissue Doppler velocity, and PAP were different between both groups. Group IIb patients had higher PAP levels, myocardial performance index and right-atrium dimension, and lower TV systolic tissue Doppler-derived systolic wave velocity, and lower TAPSE than group IIa patients

The RV basal diameter, RV wall thickness, RVOT diameters and RA area were higher and the Tei index and RVFAC were lower in group I patients than those in group IIb patients (Table 4).

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 asymmetric dimethylarginine levels between groups 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 Doppler 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 (cm^2)	18.47 ± 5.83	20 ± 3.03	0.109
RA major dimension (cm)	4.42 ± 0.86	5.3 ± 0.60	0.069
RA minor 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 volume 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	I3	I	0.06
	II16	II7	
	III1	III4	
	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 end-diastolic volume; RVESV = right-ventricle endsystolic volume; PAP = pulmoner artery pressure.

DISCUSSION

To the best of our knowledge, this is the first study which compared echocardiographic indices of right-heart and

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

Characteristics	**Group I (n = 17)**	**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 Doppler 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 (cm^2)	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	I2	I	
	II14	II7	
	III1	III4	
	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 end-diastolic volume; RVESV = right-ventricle endsystolic volume; PAP = pulmoner artery pressure.

serum-ADMA levels between patients with PVH and with PAH. This study demonstrated that patients with PAH had increased RA, RV dimensions, volumes and RV wall thickness than those with PVH. The PAP was higher in patients with PAH. The RVFAC, TAPSE and RVMPI are important echo indices for RV function. According to RVFAC, TAPSE and Tei index in our study, right-ventricle function in patients with PVH was better than those with PAH. Our results showed that ADMA levels were higher in patients with PH than those in the control group, but there was no difference between patients with PAH and with PVH.

Interestingly, although patients with PAH had worse right-heart indices and higher PAP, ADMA levels were not different between groups I and II patients. As a subgroup analysis, according to the Abbas formula (23), in the mitral stenosis group, patients with higher PVR had higher ADMA levels than those with lower PVR, although it remains to be determined whether this measurement in patients with PVH reflects the presence of PH or disease severity. Shao *et al* demonstrated that patients with systolic heart failure had elevated ADMA levels (13) which were positively correlated with systolic PAP. Altuntaş *et al* found that patients with pulmonary thromboembolism had similar ADMA levels—independent of the severity of PAP (25).

Increased ADMA levels have been shown in patients with congenital heart disease, pulmonary hypertension and valvular heart disease (26–30). 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 the ADMA levels in patients with congenital heart disease (CHD) and found that a high flow in pulmonary vascular system did not cause the increase in the ADMA levels (26). Sanli *et al* demonstrated that patients with CHD and PAH had higher ADMA levels than those with CHD but without PAH ((27). Our result is not compatible with these studies. However, our study is different in the following aspects. We compared pulmonary venous hypertensive patients with pulmonary arterial hypertensive patients. According to our results, we may suggest that ADMA is associated with the presence of PH and not the disease severity.

Pulmonary venous hypertension and PAH yield the same result: right-heart failure *via* different pathophysiological mechanisms. Yan *et al* examined the pulmonary vascular resistance and compliance in patients with mitral stenosis. It was demonstrated that PVR significantly increased in patients with rheumatic heart valve disease (28). In some patients, PVR remained 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 (28–30). The walls of pulmonary artery vessels in patients with PH secondary to rheumatic mitral stenosis may undergo structural remodelling that affects the preoperative PAP. Patients with mitral stenosis associated severe PH have decreased response to vasodilator agents due to the structural alteration of the pulmonary artery walls (3, 4, 9) Persistently elevated pulmonary venous pressure due to mitral stenosis leads the alveolar-capillary membrane to remodelling with collagen deposition (27–29, 31). Then, pulmonary vascular resistance increases due to medial hypertrophy and neointimal proliferation in distal pulmonary arteries (31).

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

The present study has some limitations. First of all, our study included a small number of patients. For an accurate evaluation, particularly for subgroup analysis, studies with a larger population are warranted. Another limitation of 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 receiving proper treatment according to guidelines (group I patients: endothelin antagonists, iloprost and sildenafil; group II patients: beta blockers and diuretic treatment). Particularly for group I patients, we did not have information about ADMA levels and echo findings before treatment. It was a major limitation, but the cessation of vasodilator treatment in these patients was not ethical. Therefore, we had to evaluate under these circumstances. In literature, there is no study which evaluates the effect of vasodilator treatment on right-heart functions and ADMA levels in patients with PAH and PVH. Therefore, further studies are warranted to identify the effect of PAH-specific treatment on ADMA levels and right-heart functions.

From this study, it can be concluded that ADMA levels were similar between patients with PVH and with PAH, although PAH caused worse right-heart functions

and elevated PAP. Therefore, we can assume that ADMA levels might be associated with the presence of PH and not with the disease severity.

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