The Effect of Pulmonary Hypertension on Left Ventricular Diastolic Function in Chronic Obstructive Lung Disease: A Tissue Doppler Imaging and Right Cardiac Catheterization Study

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ABSTRACT

Background: Pulmonary hypertension (PH) caused by chronic obstructive lung disease (COLD) essentially involves the right heart. Also left ventricular (LV) systolic and diastolic functions may be affected.

Objectives: The aim of this study was to investigate the effect of on LV diastolic function in patients with COLD.

Methods: A total of 47 patients with COLD and 20 controls were included in this study. All patients underwent Doppler echocardiography, tissue Doppler imaging examinations and right cardiac catheterization. The patients were divided into 2 subgroups according to mean pulmonary arterial pressure (mPAP): patients without PH (group 1, n = 25) and with PH (group 2, n = 22). The following measurements were taken: peak velocity of early diastolic filling (E), peak late filling with atrial contraction (A), E/A ratio, deceleration time (DT) of E, isovolumic relaxation time (IVRT), early (Em) and late (Am) diastolic mitral lateral annulus velocity. **Results:** Mitral E/A < 1 and Em < 8 cm/sec were higher in group 2 than in group 1 and the control group. There were significant correlations between mPAP and both mitral E/A (r: -0.60) and Em (r: -0.45). In multivariate model, mPAP was not found to be significant on mitral E/A ratio < 1, but there was a significant effect on mitral Em < 8 cm/sec (odds ratio [OR]: 1.14, P < 0.05).

Conclusion: This study shows that LV diastolic dysfunction in COLD is closely correlated to PH levels. Although increased mPAP may affect the mitral E/A ratio, it seems to have no effect on mitral E/A < 1, whereas it has an independent effect on Em < 8 cm/sec.

Introduction

Pulmonary hypertension (PH) is a hemodynamic problem that can result in right-sided heart failure.¹ Although PH caused by chronic obstructive lung disease (COLD) essentially involves the right heart, left ventricular (LV) function may be affected. There are also a few recent studies demonstrating that LV diastolic function may be impaired in COLD.²⁻⁴ In previous studies, the evaluation of LV diastolic function in patients with COLD and PH has primarily focused on examination of conventional mitral inflow velocity using Doppler echocardiography.²⁻⁶ Over the last few years, mitral blood flow velocity studies of diastolic function have been completed by the combined analysis of mitral inflow velocity and pulsed tissue Doppler imaging (TDI) techniques.^{7,8} The aim of this study was to determine whether LV diastolic dysfunction could be detected in COLD patients with or without PH.

Methods

Study Population

Because of difficulties in obtaining a good echocardiographic image quality in 81 patients with COLD, only 47 (29 men, 18 women; mean age 59.0 ± 8.7 y) of them had complete echocardiographic evaluation and right cardiac catheterization, and they constituted our study group. A diagnosis of COLD was made by review of the patient's history, physical examination, and pulmonary functional tests.⁹ All patients had respiratory tests including forced expiratory volume in 1 second (FEV₁) and showed an obstructive pattern by pulmonary function tests. Arterial blood was taken for measurements of pH, partial pressure of carbon dioxide blood (Paco₂), and partial pressure of arterial oxygen blood (PaO₂). A total of 20 apparently healthy and nonsmoking individuals (13 men, 7 women; mean age 57.1 ± 12.6 y) were included as the control group. All patients and controls underwent 12-lead ECG, Doppler

echocardiography, and TDI examinations. All patients and controls were in sinus rhythm. Patients were excluded for atrial fibrillation, systemic arterial hypertension, angina, myocardial infarction, valvular left heart disease, LV failure, cardiomyopathy, or complete bundle branch blocks. Medications such as inhaled steroids, β -2 agonists, theophylline, and oxygen therapy were continued during the study. We obtained informed patient consent and the ethics committee of the hospital approved the study.

Echocardiographic Examination

Echocardiograms were obtained by using the Vingmed System 5 (GE, Horten, Norway) with 2.5-MHz transducers. All individuals were studied in the left lateral recumbent position. Echocardiograms were recorded in the standard parasternal and apical views. All measurements were made during normal breathing at end-expiration and were obtained on the basis of the standards of the American Society of Echocardiography.¹⁰

Standard and Tissue Doppler Imaging

The pulsed Doppler sample volume was positioned at the mitral leaflet tips. The following measurements were taken: peak velocity of early diastolic filling (E), peak late filling with atrial contraction (A), deceleration time (DT) of E. E/A ratio was derived. Isovolumetric relaxation time (IVRT) was recorded from the apical 4-chamber view by simultaneous recording of the aortic and mitral flows. TDI was performed in the same machine. Sample volume was located at the lateral side of the mitral annulus. Early (Em) and late (Am) diastolic mitral annulus velocities and the ratio of early to late peak velocities (Em/Am) were obtained. The results of 3 heart cycles were averaged for each variable.

Cardiac Catheterization

To determine the resting mean pulmonary arterial pressure (mPAP) and pulmonary capillary wedge pressure (PCWP), right heart catheterization was performed in a standard supine position at rest and within 24 hours of the echocardiograms without any interval change in medical treatment or clinical conditions. A mPAP greater than 25 mm Hg at rest was considered as the standard for the diagnosis of PH.¹ Patients were divided into 2 subgroups: 25 patients without PH (group 1: mPAP, 17.4 ± 2.6 mm Hg) and 22 patients with PH (group 2: mPAP, 38.2 ± 10.3 mm Hg).

Statistical Analysis

Values are expressed as mean $\pm$ SD or as percentages. An analysis of variance test (ANOVA) was used for comparison of groups 1, 2, and the control group. Post hoc analysis

was done by Tukey-HSD test. Analysis was performed using the unpaired Student *t* test between 2 groups. If the variables were not normally distributed, a Mann-Whitney test was used for comparison of 2 groups. Categorical variables were examined using the χ^2 or Fisher 2-sided exact test, as appropriate. Correlations were examined by Pearson's correlation. A multivariate logistic regression test was performed to assess factors influencing LV diastolic function parameters. A *P* value $< .05$ was considered significant.

Results

Characteristics of the patients according to the mPAP are shown in Table 1. Left ventricular ejection fraction did not differ among the 3 groups, and there was no significant difference in mean PCWP between groups 1 and 2 (Table 1). Standard Doppler echocardiography and pulsed TDI analysis are shown in Table 2. Patients in group 2 had lower mitral E wave, higher mitral A wave, lower E/A ratio, longer IVRT, and lower Em than those of both group 1 and the control group. Group 2 had longer DT, higher Am,

Table 1. Characteristics of Patients with Chronic Obstructive Lung Disease and Controls

Variable	Controls (n = 20)	Group 1 (n = 25)	Group 2 (n = 22)
Age (years)	57.1 ± 12.6	57.7 ± 9.2	60.5 ± 7.9
Sex (M/F)	13/7	18/7	11/11
Body surface area (m ²)	1.71 ± 0.20	1.73 ± 0.18	1.77 ± 0.21
Systolic BP (mm Hg)	118.2 ± 13.9	122.4 ± 11.3	119.5 ± 14.5
Diastolic BP (mm Hg)	75.7 ± 8.1	76.0 ± 8.0	74.3 ± 6.6
Heart rate (bpm)	80.2 ± 11.9	81.8 ± 11.5	86.8 ± 11.4
LV ejection fraction (%)	65.4 ± 5.0	62.9 ± 5.8	61.1 ± 8.3
FEV ₁ (%)	—	55.7 ± 16.9	40.4 ± 20.0^a
PaCO ₂ (mm Hg)	—	44.1 ± 10.2	50.8 ± 13.6
PaO ₂ (mm Hg)	—	60.8 ± 11.3	52.4 ± 13.5^b
pH	—	7.41 ± 0.02	7.39 ± 0.04
PCWP (mm Hg)	—	10.4 ± 4.8	9.9 ± 5.2

Abbreviations: BP = blood pressure; FEV₁ = forced expiratory volume in 1 second; Group 1 = patients without pulmonary hypertension; Group 2 = patients with pulmonary hypertension; PaCO₂ = arterial carbon dioxide pressure; PaO₂ = arterial oxygen pressure; PCWP = pulmonary capillary wedge pressure.

^a*P* < .01 vs group 1.

^b*P* < .05 vs group 1.

Table 2. Left Ventricular Diastolic Function Parameters in Patients With Chronic Obstructive Lung Disease and Controls

Parameters	Controls (n = 20)	Group 1 (n = 25)	Group 2 (n = 22)
Mitral flow			
Peak E velocity, E (cm/s)	65.2 ± 12.7	62.5 ± 13.4	52.3 ± 13.4 ^{a,b}
Peak A velocity, A (cm/s)	64.4 ± 12.1	66.6 ± 16.9	82.9 ± 23.8 ^{a,b}
Deceleration time (ms)	187.9 ± 36.5	215.4 ± 52.3	224.7 ± 58.6
Isovolumic relaxation time (ms)	93.2 ± 10.1	97.1 ± 14.0	109.7 ± 18.2 ^{a,b}
E/A ratio	1.03 ± 0.22	0.97 ± 0.20	0.68 ± 0.26 ^c
E/A <1, n (%)	6 (30.0)	9 (36.0)	17 (77.3) ^d
Mitral annular velocity			
Early diastolic, Em (cm/s)	8.81 ± 1.70	8.68 ± 1.54	7.44 ± 1.59 ^{a,b}
Late diastolic, Am (cm/s)	10.59 ± 1.87	10.98 ± 2.42	11.25 ± 3.62
Em/Am ratio	0.85 ± 0.19	0.82 ± 0.20	0.71 ± 0.21 ^c
Em/Am <1, n (%)	13 (65.0)	18 (72.0)	20 (90.9)
Em <8 cm/sec, n (%)	5 (25.0)	7 (28.0)	13 (59.1) ^{b,e}

Abbreviations: Group 1 = patients without pulmonary hypertension; Group 2 = patients with pulmonary hypertension; E = Transmitral flow early velocity; A = Transmitral flow late velocity; Em = Early diastolic mitral annulus velocity; Am = Late diastolic mitral annulus velocity.
^a*P* < .01 vs control group.
^b*P* < .05 vs group 1.
^c*P* < .001 vs both the control group and group 1.
^d*P* < .01 vs both the control group and group 1.
^e*P* < .05 vs the control group.

and lower Em/Am ratio than those of group 1 and the control group, but not significantly (*P* > .05). The rates of mitral E/A <1 (*P* < .01) and Em <8 cm/sec (*P* < .05) were higher in group 2 than in both group 1 and the control group, but the differences between group 1 and the control group were not significant (*P* > .05). There were 3 (13.6%) patients in group 2 and 1 (4%) in group 1 who had both mitral E/A >1 and Em <8 cm/sec; but the difference between groups 1 and 2 was not significant (*P* > .05). None of the healthy individuals in the control group had mitral E/A >1 plus Em <8 cm/sec. While mean PCWP value of 4 patients with mitral E/A >1 plus Em <8 cm/sec was 15.0 ± 1.1 mm Hg,

Figure 1. Relation between mean pulmonary arterial pressure and transmitral flow velocity (early/late diastole [E/A]) in patients with chronic obstructive lung disease.

Figure 2. Relation between mean pulmonary arterial pressure and early diastolic mitral annulus velocity (Em) in patients with chronic obstructive lung disease.

the PCWP value of the remaining patients (*n* = 43) was 9.7 ± 4.9 mm Hg (*P* < .05).

Correlation Between mPAP and LV Diastolic Function Parameters

There was a significant correlation between mPAP and the following LV diastolic parameters: mitral E velocity (*r* = −0.51, *P* < .001), A velocity (*r* = 0.37, *P* < .05), mitral E/A ratio (*r* = −0.60, *P* < .001; Figure 1), IVRT (*r* = 0.41, *P* < .01), and Em (*r* = −0.45, *P* < .01; Figure 2). In addition, mPAP was correlated with PaO₂ (*r* = −0.34, *P* < .05) and FEV₁ (*r* = −0.36, *P* < .05). There were no significant correlations between mPAP and the other parameters (*P* > .05).

Multivariate Analysis

Results of the multivariate logistic regression analysis are presented in Table 3. In the multivariate model generated including age, gender, systolic blood pressure (BP), heart rate FEV₁, PaO₂, PCWP, and mPAP, none were found to not have a significant effect on mitral E/A ratio < 1. Whereas mPAP has significant effect on mitral Em < 8 cm/sec (Table 3).

Table 3. Multivariate Analysis for LV Diastolic Dysfunction Parameters in Patients With Chronic Obstructive Lung Disease

	Odds ratio (OR)	95% CI Lower	Upper	P
Mitral E/A ratio <1 (Mitral flow velocity)				
Age (years)	0.94	0.85	1.04	.28
Gender	3.09	0.58	16.45	.18
Systolic BP (mm Hg)	0.96	0.89	1.03	.28
Heart rate (bpm)	0.99	0.93	1.06	.86
FEV ₁	1.04	0.99	1.09	.10
PaO ₂ (mm Hg)	1.05	0.98	1.12	.13
PCWP (mm Hg)	1.12	0.93	1.34	.22
mPAP	0.97	0.89	1.05	.48
Early diastolic velocity (Em) < 8 cm/sec (mitral lateral annulus)				
Age (years)	0.95	0.86	1.05	.35
Gender	1.19	0.18	7.63	.85
Systolic BP (mm Hg)	0.95	0.88	1.02	.14
Heart rate (bpm)	1.02	0.95	1.10	.56
FEV ₁	1.00	0.96	1.05	.84
PaO ₂ (mm Hg)	1.02	0.96	1.09	.54
PCWP (mm Hg)	1.10	0.93	1.31	.27
mPAP	1.14	1.03	1.26	.012
Abbreviations: BP = blood pressure; CI = confidence interval; FEV ₁ = forced expiratory volume in 1 second; Mitral A = peak late filling with atrial contraction; Mitral E = peak velocity of early diastolic filling; mPAP = mean pulmonary arterial pressure; PaO ₂ = arterial oxygen pressure; PCWP = pulmonary capillary wedge pressure.				

Discussion

This study is the first, to our knowledge, that performed an invasive hemodynamic study (right cardiac catheterization) in patients with COLD including LV diastolic function that was studied by a combined analysis of conventional mitral inflow velocities and mitral annulus velocities. In previous studies, the evaluation of LV diastolic function in patients with COLD has primarily focused on examination of conventional mitral inflow velocity using Doppler echocardiography,^{2–6} and tricuspid regurgitation flow was identified and systolic pulmonary artery pressure was measured by means of the Bernoulli equation ($P = 4 V^2$). Whereas, in the present study we used the mean pressure

of the pulmonary artery, and mPAP >25 mm Hg was considered as the standard for the diagnosis of PH. Also, we measured the mean PCWP of these patients. Ozer et al⁴ studied the mitral inflow velocity using Doppler echocardiography and the flow propagation velocity using color Doppler M-mode image in patients with COLD and PH. They found that while patients without PH had normal LV diastolic function, patients with PH had abnormal LV diastolic function parameters. In the present study, although patients with PH had lower mitral E and higher A waves, lower E/A ratio and longer IVRT when compared to both the patients without PH and the healthy volunteers, the differences between the patients without PH and the healthy volunteers were not significant. Thus, our study confirmed that the changes occurred in the LV filling profile in COLD with PH. However, interpretation of the patterns derived from transmitral Doppler flow is often limited by the influence of hemodynamic factors such as heart rate, afterload, preload, and intravascular volume.^{7,11,12} Right ventricular (RV) pressure overload leads to a leftward shift of the interventricular septum, resulting in impaired LV early filling as seen in pulmonary hypertensive patients. In these patients, the restraining influence of the pericardium and reduction in RV output could result in decreased LV preload and reduced LV filling patterns. But, the substantial contribution to this impaired function is due to the septum delaying the opening mitral valve and the start of filling.^{2,3}

TDI Analysis in Patients With COLD

Mitral annulus motion is less load dependent than conventional mitral inflow variables and its assessment by TDI appears to be useful for evaluating diastolic function, especially in the detecting a pseudonormalization pattern of mitral inflow.^{7,8,13} Mitral annulus velocities primarily reflect longitudinal motion due to the longitudinally directed fibers, and reflect global LV function.^{14,15} Garcia et al⁷ reported the Em velocity of 8 cm/sec as a cut off value in determining LV diastolic dysfunction. Thereby, the TDI method is a very valuable tool for assessing global LV diastolic function in pathological conditions. In this study, although we found that the Em velocity was significantly reduced in patients with PH when compared with both the patients without PH and the control group, there was no significant difference between the patients without PH and the control group. We also used Em velocity of 8 cm/sec as a cut off value in determining LV diastolic dysfunction. In our study, the rate of mitral E/A <1 and Em <8 cm/sec were higher in patients with PH than those without PH and the control group. However, in patients with PH, Em <8 cm/sec was lower than mitral E/A <1. Similarly, Sohn et al⁸ demonstrated a significant reduction in mitral E wave and E/A ratio after nitroglycerin infusion in patients with normal or pseudonormal filling at baseline. In contrast, they found no significant changes in the Em velocity. In this study, we

observed that 3 (13.6%) patients with PH and 1 (4%) patient without PH had both mitral E/A >1 and Em <8 cm/sec (pseudonormal filling pattern). However, none of healthy individuals in the control group had a pseudonormal filling pattern. Moreover, the mean PCWP value of patients with a pseudonormal pattern was higher than in those without a pseudonormal pattern. This finding shows increased left atrial pressure in the pseudonormal filling pattern. Again, this result confirms that changes in Em velocity are less sensitive to preload changes. On the other hand, we found an inverse correlation ($r = -0.45$) between mPAP and Em velocity. However, this correlation is not stronger than the correlations between mPAP and mitral E/A ($r = -0.60$), and mitral E velocity ($r = -0.51$), so mitral E/A ratio may be affected more by increased mPAP. On the other hand, we found that in the model generated by including our main interest variables (Table 3), none of the factors did not have an influence on the mitral E/A ratio <1, whereas only mPAP, independently, has an effect on the mitral Em <8 cm/sec. In our study group, COLD patients, there were a total of 4 (8.5%) patients with (3) and without (1) PH that had the pseudonormal filling pattern, which can partly explain the reason for this result. Ruan et al,¹⁶ in patients with idiopathic PH with invasive measurements, showed that TDI of lateral mitral annulus can predict the presence of normal or reduced mean PCWP.

Study Limitations

In this study, there are a number of variables affecting trans-mitral Doppler parameters, such as age, heart rate, and loading conditions. In addition, invasive and echocardiographic examinations were not performed simultaneously. However, there were no significant differences of heart rate and systemic arterial blood pressure in these examinations between the groups. Again, we did not find significant differences between the patients and control groups in terms of age, gender, and body surface area. Another limitation, in some patients, is that a dorsal and left-lateral displacement of the left ventricle occurs. Thus, the optimal transducer position could not be achieved for alignment with mitral inflow, which is directed to the lateral wall of the left ventricle. In these patients, a correction was made for the angle between the Doppler echocardiographic beam and flow direction. Again, we measured the pulsed TDI velocities at the lateral side of mitral annulus because the septal side approach has the potential disadvantage of being affected by impaired RV function.

Clinical Implications

A combined analysis of mitral flow velocities and mitral lateral annulus velocity has a useful application in the evaluation of LV diastolic dysfunction. The presence of PH in COLD patients, independently, leads to functional diastolic impairment of the left ventricle. Again, it may be the

discordance between conventional mitral inflow and mitral lateral annulus velocities in some of patients with COLD. Also mitral Em velocity may be less than 8 cm/sec in some COLD patients without PH (there were 7 [28%] patients in our study group; Table 2). In these patients, some factors such as intrinsic LV abnormalities may be partly responsible for LV diastolic dysfunction. For example, chronic hypoxia in patients with COLD may have a detrimental effect in energy production of the myocardium at the cellular level,¹⁷ and may be partly responsible for impaired relaxation in both COLD and PH patients. Also a pseudonormal filling pattern may be partly responsible for impaired relaxation of the left ventricle in some COLD patients with PH.

Conclusion

The present study confirms that functional diastolic impairment of the left ventricle in COLD patients is closely correlated to PH levels and shows that some patients with COLD and PH have a pseudonormal filling pattern. In COLD patients, although increased mPAP may affect the mitral E/A ratio, it may seem to have no effect on mitral E/A <1, whereas increased mPAP has an independent effect on the lateral mitral annulus Em <8 cm/sec.

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