

# Concordance between Doppler and pulsed-wave Doppler tissue imaging in estimation of the degree of left ventricular dysfunction and correlating it to the degree of chronic obstructive pulmonary disease



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**Objective:** As a consequence of leftward shift of the interventricular septum and of pericardial restraint, related to the degree of right ventricular dilation, alveolar hypoxia and related pulmonary vascular changes, left ventricular function is influenced by chronic obstructive pulmonary disease (COPD). The aim of this study was to assess the prevalence of echocardiographic abnormalities by conventional echocardiography and Doppler tissue imaging (DTI) in COPD patients according to the degree of disease severity.

**Methods:** We enrolled forty consecutive patients with COPD and twenty matched control. Twenty of the patients were suffering from mild form of COPD, twenty were suffering from severe form of COPD as decided by pulmonary function test and arterial blood gases and twenty apparently healthy non COPD control persons were subjected to echocardiographic assessment to left ventricular diastolic and systolic functions by conventional echocardiography and DTI at the mitral annulus.

**Results:** There were no significant statistical difference between the three groups as regards the age and the gender. There were significant statistical differences between the patients and the control as regards the diastolic functions of the left ventricle. E and A waves obtained by conventional Doppler and by DTI showed significant statistical difference between mild, severe forms of COPD and control subjects. The degree of diastolic dysfunction increased significantly with increase of the severity of COPD.

**Conclusion:** Left ventricular diastolic function is significantly affected in patients with COPD and the degree of affection is related to the severity of COPD.

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## Introduction

Chronic obstructive pulmonary disease (COPD) is a common cause of pulmonary arterial hypertension. Increased right ventricular afterload caused by pulmonary hypertension in patients with COPD eventually leads to dilation of the right ventricle (RV), with or without hypertrophy. There are several studies demonstrating that patients with COPD have RV systolic and/or diastolic dysfunction [1,2]. Previous studies have shown that patients with COPD also have left ventricular (LV) diastolic dysfunction [3,4]. Impairment of LV diastolic filling is related to the prolongation of LV isovolumic relaxation and the impediment of rapid filling, as a result of leftward interventricular septal shift and distortion of early diastolic geometry [5,6]. Mechanisms of impaired LV filling in very severe COPD include alveolar hypoxia, related pulmonary vascular changes, and pulmonary hyperinflation. Alveolar hypoxia causes pulmonary artery vasoconstriction and vascular remodeling [7]. Inflammation is considered one of the systemic manifestations of COPD and provides an alternative hypothesis for the explanation of the relationship between airflow limitation and cardiovascular risk [8].

Doppler tissue imaging (DTI) is evolving as a useful echocardiographic tool for quantitative assessment of left ventricular (LV) systolic and diastolic function. Studies have explored the prognostic role of DTI-derived parameters in major cardiac diseases, such as heart failure, acute myocardial infarction, and hypertension. In these conditions, myocardial mitral annular or basal segment systolic and early diastolic velocities have been shown to predict mortality or cardiovascular events [9].

The aim of this study is to assess the prevalence of echocardiographic abnormalities by conventional echocardiography and Doppler tissue imaging in COPD patients according to the degree of disease severity.

## Methods

### *Patient selection*

The study included 40 consecutive patients from outpatient clinics, while the control group comprised 20 age and sex-matched, healthy subjects who were not COPD patients. COPD diagnosis was confirmed according to the guidelines established in the Global Initiative for Chronic

### Abbreviations

COPD	chronic obstructive pulmonary disease
DTI	Doppler tissue imaging
LV	left ventricle
RV	right ventricle
GOLD	Global Initiative for Chronic Obstructive Lung Disease
FEV <sub>1</sub>	Forced expiratory volume
FVC	flow-volume curves
IC	inspiratory capacity
TLC	total lung capacity
PFTs	pulmonary function tests

Obstructive Lung Disease (GOLD). COPD was categorized according to the GOLD stages, considering the Forced expiratory volume (FEV<sub>1</sub>) (% predicted) and arterial blood gas values [10,11].

Before inclusion, an informed written consent was obtained from each patient after full explanation of the study protocol. The protocol was reviewed and approved by our local institutional human research committee, which conforms to the ethical guidelines of the 1975 Declaration of Helsinki, revised in 2002.

The exclusion criteria consisted of a primary diagnosis of other respiratory diseases such as asthma, restrictive disorders, tuberculosis sequelae, or interstitial fibrosis, as well as sleep apnea/hypopnea syndrome, or lung cancer. In addition, a primary diagnosis of unstable angina, congestive heart failure (New York Heart Association class III or IV) or other chronic diseases, such as uncontrolled diabetes mellitus, kidney or liver failure and cancer, also constituted grounds for exclusion. Patients were assessed on three different days of the same week through clinical evaluations, spirometry, and echocardiogram tests.

### *Pulmonary function tests*

Pulmonary function tests (PFT) were carried out in the pulmonary function unit using the flow-volume curves (FVC). Subjects performed the FVC maneuver by inhaling fully and then exhaling as rapidly as possible; to complete the loop, subjects inhaled as rapidly as possible from the maximal expiratory level back to maximal inhalation. An arterial sample was obtained from the radial artery to perform arterial blood gases (ABGs) for measuring the arterial oxygen tension (PO<sub>2</sub>).

COPD patients were divided into two groups, each group comprising 20 patients. The study also

included a control group of 20 subjects with normal pulmonary function tests.

The first group included mild cases of COPD, characterized by  $FEV_1/FVC < 70\%$ ,  $FEV_1 \geq 50\%$  of predicted, with or without chronic symptoms. The second group included severe and very severe cases of COPD, characterized by  $FEV_1/FVC < 70\%$ ,  $FEV_1 < 50\%$  of predicted, with or without chronic symptoms. Control subjects had normal PFT showing  $FEV_1/FVC > 70\%$ ,  $FEV_1 > 80\%$  of predicted.

### Echocardiography

Echocardiography was performed on all subjects according to the same protocol with use of GE Medical System Vivid 7 ultrasound machine equipped with 2–4 MHz sector transducer probe. With participants positioned in left lateral decubitus and monitored using an electrocardiographic lead, the following echocardiographic cuts were performed: short parasternal axis to measure ventricles, left atrium and apical two, four and five chambers to evaluate cavities and systolic and diastolic functions of ventricles. All measurements were performed in accordance with the guidelines/recommendations of American Society of Echocardiography/European Association of Echocardiography [12]. The echocardiographic analysis was performed blinded to COPD severity.

Parameters obtained through parasternal approaches in the M-mode projection were analyzed: left ventricular end diastolic diameter (EDD), left ventricular end systolic diameter (ESD), interventricular septum (IVS), left ventricular posterior wall thickness (PW), right ventricular end diastolic diameter (RVEDD), right ventricular end systolic diameter (RVESD), and left atrial diameter (LA).

The assessment of the left ventricular systolic function consisted of left ventricular ejection fraction (EF%) obtained according to Simpson's formula.

To assess left ventricular diastolic function, isovolumetric relaxation time (IVRT), which is the interval from the aortic valve closure signal to the mitral valve opening signal, and the following transmitral inflow parameters were measured (pulsed wave Doppler registration with gate placed at the tip of open mitral valve leaflets): peak velocity of the early E-wave transmitral flow (E), peak velocity of late A-wave transmitral flow (A), and the ratio (E/A) was derived. Pressure half time (PHT), which is the half time of the deceleration of the early diastolic transmitral flow and

which reflects the rapidity of the pressure gradient drop from LA to LV, was obtained.

Tricuspid regurgitant (TR) flow was identified in continuous Doppler mode from the apical four chamber view. The Bernoulli equation was used to calculate the systolic tricuspid gradient that equals  $4V^2$ . Right atrial was arbitrarily fixed to a value of 100 mmHg and right ventricular systolic pressure (RVSP) was obtained as = gradient RV/RA + 10. Pulmonary acceleration time (PAT) was defined as the time from the onset of pulmonary flow to the maximum pulmonary velocity.

### Mitral annular velocity by DTI

We used the same GE Vivid Seven machine using a commercially available imaging system equipped with a 2–4 MHz transducer and secondary harmonic imaging to optimize endocardial border visualization. From the apical four and two chamber views, the longitudinal mitral annular velocities were recorded from septal, lateral, inferior and anterior LV sites using PW-DTI. A mean value from the above four sites was used to assess global systolic and diastolic function. Three major velocities were taken into account: the positive peak systolic velocity when the mitral ring moved towards the cardiac apex due to longitudinal contraction of the LV, and two negative diastolic velocities when the mitral annulus moved towards the base away from the apex; one during the early phase of diastole, and the other in the late phase of diastole. A mean of three consecutive cycles was used to calculate all echo-Doppler parameters.

### Statistical analysis

Data are presented as mean  $\pm$  SD. The Chi-squared test was used to compare differences between proportions. The Analysis of variance (ANOVA) test was used for analysis of continuous data. The Bonferroni test was performed for comparison between each two of the three variables with  $p$  value  $< 0.05$  as per ANOVA test. A probability value of  $p < 0.05$  was considered statistically significant. Analyses were performed with SPSS version 12.0 statistical package (SPSS Inc., Chicago, IL, USA). Differences were considered significant if the null hypothesis could be rejected at the .05 probability level.

### Results

There was no significant statistical difference between the three groups as regards age and sex. The mean age was  $52.75 \pm 5.11$  years for patients with mild COPD,  $50.30 \pm 4.40$  for patients

Table 1. Baseline characteristics in patients with COPD and control subjects.

	Control	Mild	Severe
Age	51.40 ± 3.89	52.75 ± 5.11	50.30 ± 4.40
Male	10 (50%)	10 (50%)	9 (45%)
Heart rate $\Omega$	71.80 ± 4.41	82.35 ± 4.05	84.85 ± 3.77
Diabetes mellitus	0 (0%)	1 (5%)	2 (10%)
Dyslipidemia	2 (10%)	3 (15%)	3 (15%)
Systolic blood pressure	116.01 ± 15.12	114.10 ± 19.32	120.21 ± 16.21
Diastolic blood pressure	72.65 ± 8.20	74.67 ± 11.21	74.56 ± 10.32

$\Omega = p < 0.001$  between the three groups.

with severe COPD and 51.40 ± 3.89 for control group with  $p > 0.05$ . As regards the gender we had ten male patients with mild COPD, nine male patients with severe COPD and ten males as control subjects with  $p > 0.05$ .

Heart rate was 82.35 ± 4.05 bpm in patients with mild COPD, 84.85 ± 3.77 bpm in patients with severe COPD and 71.80 ± 4.41 bpm in control group with  $p < 0.001$  (Table 1).

As regards LV dimensions systolic function and left atrial diameter there were no significant statistical difference between the three groups. The condition was totally different regarding the diastolic function of LV and all the echocardiographic and Doppler function of the right side e.g. RVEDD, RVESD, TR, RVSP and PAT (Table 2).

The LV diastolic function parameters in the studied groups are shown in Table 3, the mitral

Table 2. Echocardiographic parameters in patients with COPD and control subjects.

	Control	Mild	Severe	<i>p</i> value
EDD (mm)	47.10 ± 3.28	47.21 ± 3.80	48.20 ± 4.58	0.678
ESD (mm)	29.70 ± 3.68	30.95 ± 3.72	31.20 ± 4.00	0.588
IVS (mm)	8.50 ± 1.08	9.20 ± 1.19	9.45 ± 1.14	0.114
PW (mm)	8.50 ± 1.26	9.25 ± 1.06	9.25 ± 1.11	0.183
RVEDD(mm) <sup>*,#</sup>	20.00 ± 3.19	35.05 ± 5.01	37.80 ± 6.46	<0.001
RVESD (mm) <sup>*,#</sup>	15.40 ± 2.79	25.05 ± 4.71	26.35 ± 4.93	<0.001
EF (%)	66.30 ± 5.79	63.05 ± 5.77	64.35 ± 5.85	0.357
LA (mm)	34.50 ± 2.22	35.30 ± 3.41	36.65 ± 3.32	0.184
RVSP <sup>*,#,@</sup>	24.40 ± 3.06	44.35 ± 8.20	57.25 ± 10.44	<0.001
PAT (msec) <sup>*,#,@</sup>	130.00 ± 14.90	81.00 ± 7.88	62.00 ± 15.76	<0.001

Variables are expressed as mean ± standard deviation.

EDD = Left ventricular end diastolic dimension, ESD = Left ventricular end systolic dimension, IVS = Interventricular septum thickness, PW = Posterior wall thickness, RVEDD = Right ventricular end diastolic dimension, RVESD = Right ventricular end systolic dimension, EF = Ejection fraction, LA = Left atrium, RVSP = Right ventricular systolic pressure, PAT = Pulmonary acceleration time.

\* Significant *p* value between control group and mild group.

# Significant *p* value between control group and severe group.

@ Significant *p* value between mild group and severe group.

Table 3. Doppler parameters: Left ventricular filling in patients with COPD and control subjects.

	Control	Mild	Severe	<i>p</i> value
MVE (cm/sec) <sup>*,#</sup>	79.90 ± 9.80	62.85 ± 13.16	64.85 ± 14.26	0.004
MVA (cm/sec) <sup>*,#,@</sup>	61.10 ± 9.31	68.10 ± 13.30	79.75 ± 11.58	<0.001
MVE/A <sup>*,#,@</sup>	1.32 ± 0.18	0.89 ± 0.09	0.76 ± 0.09	<0.001
IVRT (msec) <sup>*,#</sup>	81.60 ± 7.53	101.50 ± 7.79	105.60 ± 7.13	<0.001
PHT (msec)	75.50 ± 9.84	77.75 ± 10.81	68.20 ± 14.99	0.056

Variables are expressed as mean ± standard deviation.

MVE = Mitral valve E wave, MVA = Mitral valve A wave, MVE/A = Mitral valve E/A ratio, IVRT = isovolumetric relaxation time, PHT = Pressure half time.

\* Significant *p* value between control group and mild group.

# Significant *p* value between control group and severe group.

@ Significant *p* value between mild group and severe group.

Table 4. Mitral annular pulsed wave tissue Doppler in patients with COPD and control subjects.

	Control	Mild	Severe	p value
LAT S' (cm/sec)	14.27 ± 0.97	13.62 ± 1.66	13.68 ± 0.73	0.370
LAT E' (cm/sec) <sup>*,#,@</sup>	12.24 ± 1.70	7.74 ± 0.49	6.37 ± 0.56	<0.001
LAT A' (cm/sec) <sup>*,#,@</sup>	6.81 ± 0.52	11.01 ± 0.63	14.19 ± 1.65	<0.001
SEP S' (cm/sec)	7.86 ± 0.67	7.94 ± 0.64	7.80 ± 0.54	0.786
SEP E' (cm/sec) <sup>*,#,@</sup>	12.19 ± 1.23	7.60 ± 0.33	6.37 ± 0.56	<0.001
SEP A' (cm/sec) <sup>*,#,@</sup>	6.91 ± 0.65	11.59 ± 0.68	14.22 ± 1.85	<0.001
ANT S' (cm/sec)	12.48 ± 0.38	11.91 ± 0.61	11.99 ± 0.57	0.033
ANT E' (cm/sec) <sup>*,#,@</sup>	12.24 ± 1.70	7.90 ± 0.53	6.33 ± 0.54	<0.001
ANT A' (cm/sec) <sup>*,#,@</sup>	6.96 ± 0.90	11.72 ± 0.66	14.60 ± 1.16	<0.001
INF S' (cm/sec)	9.91 ± 0.62	10.26 ± 0.98	10.02 ± 0.55	0.439
INF E' (cm/sec) <sup>*,#,@</sup>	14.14 ± 0.76	7.69 ± 0.49	5.88 ± 0.52	<0.001
INF A' (cm/sec) <sup>*,#,@</sup>	7.82 ± 0.37	11.05 ± 1.12	15.30 ± 2.49	<0.001
TOTAL S' (cm/sec)	11.13 ± 0.27	10.90 ± 0.53	10.91 ± 0.38	0.349
TOTAL E' (cm/sec) <sup>*,#,@</sup>	12.70 ± 0.98	7.73 ± 0.20	6.24 ± 0.37	<0.001
TOTAL A' (cm/sec) <sup>*,#,@</sup>	7.12 ± 0.39	11.34 ± 0.57	14.58 ± 1.14	<0.001
TOTAL E'/A' (cm/sec) <sup>*,#,@</sup>	1.78 ± 0.12	0.68 ± 0.02	0.43 ± 0.04	<0.001

Variables are expressed as mean ± standard deviation.

LAT = Lateral mitral annular velocities, SEP = Septal mitral annular velocities, ANT = anterior mitral annular velocities, INF = inferior mitral annular velocities. S' = Positive peak systolic velocity, E' = Negative early diastolic velocity, A' = negative late diastolic velocity.

\* Significant p value between control group and mild group.

# Significant p value between control group and severe group.

@ Significant p value between mild group and severe group.

inflow velocities E, A, E/A and IVRT differed significantly in patients with COPD compared with the control subjects. E/A ratio was significantly lower in patients with COPD  $p < 0.001$ .

Multiple comparisons were done to evaluate the significant statistical difference between the three groups to determine the relation between each two groups individually.

The single values and the mean values obtained by pulsed wave tissue Doppler imaging obtained at the four sites of the mitral annulus revealed that there was no significant statistical difference between the COPD patients and the control group as regards the systolic function of the LV. Regarding the diastolic functions of the LV, there were highly significant statistical difference between the COPD patients and the control group. When the diastolic functions of the LV were studied in details, there were highly significant statistical difference between the three groups individually as shown in Table 4.

## Discussion

Echocardiography is the most common and feasible non-invasive method to assess LV diastolic function. In our study, E/A ratio was significantly lower and IVRT was significantly longer in patients with COPD. With DTI, there were significant statistical differences between control subjects and COPD patients in E', A' and E'/A' ratio of the mitral annular velocities.

The E/A ratio mainly represents a measurement of LV filling. According to previous studies

performed in COPD patients, a lower E/A ratio means an increased atrial contribution to this filling. This occurs in both the presence and absence of elevated pulmonary artery pressure. However, LV diastolic dysfunction in COPD could be the result of decreased preload or pathological myocardial compliance. It is unknown which echocardiographic parameters are best to measure LV diastolic dysfunction [13]. In a population-based study of subjects without very severe COPD, Barr et al [14] found that percent emphysema and the severity of airflow obstruction were associated with significant decrements in left ventricular filling and cardiac output. They speculated that the subclinical loss of the pulmonary capillary bed in patients with mild emphysema was responsible for the left ventricular hypofilling, whereas hyperinflation of the lung only had a role in very severe COPD [14]. Waltz et al [15] found hyperinflation of the lung to have a stronger association with the left ventricular end-diastolic diameter than airflow obstruction or the diffusion capacity for carbon monoxide in 138 patients with COPD ranging from mild to severe. Therefore, it was assumed that hyperinflation had an effect on decreasing pulmonary vascular compliance that was mediated by an elevated intrinsic positive end-expiratory pressure [16], and that, in turn, led to an increased right ventricular load, a reduced right ventricular stroke volume, and left ventricular hypofilling. In line with this assumption, it was found that right ventricular ejection time as a surrogate for right ventricular stroke volume was clearly related to

hyperinflation [17]. Even though the pathophysiology of left ventricular hypofilling is not fully understood, the condition was clinically relevant for patients with COPD, since it independently affected their physical activity and exercise tolerance [18]. Reversible ischemic defects are quite common (50%) in advanced COPD patients with LV diastolic dysfunction, without the presence of common risk factors. This association needs further evaluation [19].

Unlike our study and previous reports, Schoos et al [20] did not find decreasing E/A and increasing deceleration time of *E* with increasing hyperinflation [15] or COPD severity [21], nor did they find decreasing E/A with increasing SPAP [22]. In their overall population, E/A and DT were numerically very similar compared to normal individuals [23]. However, diastolic mitral Doppler data in COPD could be interpreted as a sign of low LV preload and not necessarily an intrinsic impairment in LV relaxation/compliance. Decreasing E/E' with increasing COPD severity indicates lower left ventricular filling pressures [23], which lends support to the concept of reduced preload in COPD. In the study by Schoos et al [20], the design was cross-sectional, making firm conclusions about causality impossible. Further, Schoos et al did not have a control group, and therefore required the use of reference values from the literature.

Several factors can be put forward to explain changes in LV filling profile, some of which are well evidenced by Doppler echocardiography. The first and the most important is the significantly increased HR in the COPD group. Tachycardia shortened the diastolic filling period, and atrial contraction may have occurred before the early filling was completed. The transmitral A peak velocity will be higher than it would be if HR were slower. This tachycardia may be due to multiple causes, including hypoxemia or medications [24]. All our patients presented with marked hypoxemia, and COPD patients are known to show a more pronounced reaction to low blood oxygen content. Medications given to the COPD patients included beta2-agonist, theophylline or atropine, all potentially responsible for tachycardia. This decreased LV preload in stable patients with COPD has rarely been reported in the literature, and may have contributed to the acceleration of the HR. Reduced LV preload could be due to reduced venous return flow or to hypovolemia. Obstruction of the bronchi, severe in our COPD patients, may have increased intrinsic positive

end-expiratory pressure and limited the venous return blood flow [25].

Studies have evaluated patients who were hospitalized for exacerbation of COPD associated with diastolic dysfunction, and have shown that left diastolic dysfunction increased the risk of hospitalization for exacerbation [26]. These data reinforce the importance of left ventricular diastolic evaluation in COPD patients.

Mitral annular or basal LV velocities reflect the long-axis motion of the ventricle, which is an important component of LV systolic and diastolic function. Subendocardial fibers make a substantial contribution to long-axis function, and these are particularly susceptible to disturbance by various diseases and pathologies [9].

The evaluation of LV diastolic function in patients with COPD has primarily focused on examination of conventional mitral inflow velocity using Doppler echocardiography. 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 [27].

Mitral annulus motion is less load dependent than conventional mitral inflow variables, and its assessment by DTI appears to be useful for evaluating diastolic function, especially in detecting a pseudonormalization pattern of mitral inflow. Mitral annulus velocities primarily reflect longitudinal motion due to longitudinally directed fibers, but also reflect global LV function. It was reported that E velocity of DTI of 8 cm/sec was used as a cut-off value in determining LV diastolic dysfunction. The DTI method is therefore a valuable tool for assessing global LV diastolic function in pathological conditions. In patients with idiopathic pulmonary hypertension as proved with invasive measurements, DTI of lateral mitral annulus was able to predict the presence of normal or reduced mean pulmonary capillary wedge pressure [28].

The limitations of this study are the small sample size. In addition, strain and strain rate were not performed. Body plethysmography was not performed, and the diffusion capacity or the ratio of inspiratory capacity (IC) to total lung capacity (TLC) as well as residual volume are unknown. These parameters allow judgement on the degree of lung hyperinflation, which is known to influence heart function – both systolic and diastolic. Further studies are needed to detect additional abnormalities and throw light on how to deal with them in order to improve morbidity and mortality rates of COPD patients.

In conclusion, we found significant statistical difference between COPD patients, control subjects, and patients with mild and severe COPD using PFTs for left ventricular diastolic function determined by both conventional Doppler and DTI. We demonstrated that the degree of LV diastolic dysfunction is related to the degree of COPD severity, as shown in Table 4.

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